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- (54) Titre : POLYMERES BIODEGRADABLES POLYMERISABLES CONTENANT DES LIAISONS CARBONATES OU DIOXANONES  
(54) Title: POLYMERIZABLE BIODEGRADABLE POLYMERS INCLUDING CARBONATE OR DIOXANONE LINKAGES

(57) **Abrégé/Abstract:**

Water-soluble macromers including at least one hydrolysable linkage formed from carbonate or dioxanone groups, at least one water-soluble polymeric block, and at least one polymerizable group, and methods of preparation and use thereof are described. The macromers are preferably polymerized using free radical initiators under the influence of long wavelength ultraviolet light or visible light excitation. Biodegradation occurs at the linkages within the extension oligomers and results in fragments which are non-toxic and easily removed from the body. The macromers can be used to encapsulate cells, deliver prophylactic, therapeutic or diagnostic agents in a controlled manner, plug leaks in tissue, prevent adhesion formation after surgical procedures, temporarily protect or separate tissue surfaces, and adhere or seal tissues together.



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<p>(21) International Application Number: PCT/US97/16857</p> <p>(22) International Filing Date: 23 September 1997 (23.09.97)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>710,689</td> <td>23 September 1996 (23.09.96)</td> <td>US</td> </tr> <tr> <td>60/054,849</td> <td>6 August 1997 (06.08.97)</td> <td>US</td> </tr> </table> <p>(60) Parent Applications or Grants</p> <p>(63) Related by Continuation</p> <table border="0"> <tr> <td>US</td> <td>08/710,689 (CIP)</td> </tr> <tr> <td>Filed on</td> <td>23 September 1996 (23.09.96)</td> </tr> <tr> <td>US</td> <td>60/054,849 (CIP)</td> </tr> <tr> <td>Filed on</td> <td>6 August 1997 (06.08.97)</td> </tr> </table> <p>(71) Applicant: FOCAL, INC. [US/US]; 4 Maguire Road, Lexington, MA 02173 (US).</p> <p>(72) Inventors: JARRETT, Peter, K.; 353 Willis Road, Sudbury, MA 01776 (US). SAWHNEY, Amarpreet; 164 Springs Road, Bedford, MA 01730 (US). COURY, Arthur, J.; 154 Warren Avenue, Boston, MA 02116 (US). RUDOWSKY, Ronald, S.; 10 Redhorse Path, Sudbury, MA 01776 (US).</p>	710,689	23 September 1996 (23.09.96)	US	60/054,849	6 August 1997 (06.08.97)	US	US	08/710,689 (CIP)	Filed on	23 September 1996 (23.09.96)	US	60/054,849 (CIP)	Filed on	6 August 1997 (06.08.97)	<p>POWELL, Michelle, D.; 15 Elm Street, Tewksbury, MA 01876 (US). AVILA, Luis, Z.; 23 Rockaway Lane, Arlington, MA 02174 (US). ENSCORE David, J.; 2 Red Oak Drive, Sudbury, MA 01776 (US). GOODRICH, Stephen, D.; 14 North Washington #3, Woburn, MA 01801 (US). NASON, William, C; 133 Westview Drive, Westford, MA 01886 (US). YAO, Fei; 260 Candlestick Road, North Andover, MA 01845 (US). WEAVER, Douglas; 17 Old Stagecoach Road, Bedford, MA 01730 (US). BARMAN, Shikha, P.; 31 Marion Road, Bedford, MA 01730 (US).</p> <p>(74) Agents: PABST, Patrea, L. et al.; Arnall Golden &amp; Gregory, 2800 One Atlantic Center, 1201 West Peachtree Street, Atlanta, GA 30309-3450 (US).</p> <p>(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
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<p>Water-soluble macromers including at least one hydrolysable linkage formed from carbonate or dioxanone groups, at least one water-soluble polymeric block, and at least one polymerizable group, and methods of preparation and use thereof are described. The macromers are preferably polymerized using free radical initiators under the influence of long wavelength ultraviolet light or visible light excitation. Biodegradation occurs at the linkages within the extension oligomers and results in fragments which are non-toxic and easily removed from the body. The macromers can be used to encapsulate cells, deliver prophylactic, therapeutic or diagnostic agents in a controlled manner, plug leaks in tissue, prevent adhesion formation after surgical procedures, temporarily protect or separate tissue surfaces, and adhere or seal tissues together.</p>															

## **POLYMERIZABLE BIODEGRADABLE POLYMERS INCLUDING CARBONATE OR DIOXANONE LINKAGES**

### **Field of the invention**

The present invention relates to improved photopolymerizable  
5 biodegradable hydrogels for use as tissue adhesives, coatings, sealants and  
in controlled drug delivery devices. The improved materials incorporate  
carbonate and/or dioxanone linkages. These biodegradable linkages allow  
improved control of various properties of the macromers, particularly  
increasing viscosity while preserving biodegradability.

### **Background of the Invention**

U.S. Patent No. 5,410,016 to Hubbell et al. discloses  
biocompatible, biodegradable macromers which can be polymerized to  
form hydrogels. The macromers are block copolymers that include a  
biodegradable block, a water-soluble block with sufficient hydrophilic  
15 character to make the macromer water-soluble, and one or more  
polymerizable groups. The polymerizable groups are separated from each  
other by at least one degradable group, Hubbell specifically discloses using  
polyhydroxy acids, such as polylactide, polyglycolide and polycaprolactone  
as the biodegradable polymeric blocks. One of the disclosed uses for the  
20 macromers is to plug or seal leaks in tissue.

Other hydrogels have been described, for example, in U.S. Patent  
No. 4,938,763 to Dunn et al., U.S. Patent Nos. 5,100,992 and 4,826,945 to  
Cohn et al., U.S. Patent Nos. 4,741,872 and 5,160,745 to De Luca et al.,  
U.S. Patent No. 5,527,864 to Suggs et al., and U.S. Patent No. 4,511,478  
25 to Nowinski et al. Methods of using such polymers are described in U.S.  
Patent No. 5,573,934 to Hubbell et al. and PCT WO 96/29370 by Focal.

While numerous references disclose using homopolymers and  
copolymers including carbonate linkages to form solid medical devices,  
such as sutures, suture coatings and drug delivery devices (see, for  
30 example, U.S. Patent No. 3,301,824 to Hostettler et al., U.S. Patent No.  
4,243,775 to Rosensaft et al., U.S. Patent No. 4,429,080 to Casey et al.,

U.S. Patent No. 4,716,20 to Casey et al., U.S. Patent No. 4,857,602 to Casey et al., U.S. Patent No. 4,882,168 to Casey, EP 0 390 860 B1 by Boyle et al., U.S. Patent No. 5,066,772 to Tang et al., U.S. Patent No. 5,366,756 to Chesterfield et al., U.S. Patent No. 5,403,347 to Roby et al.  
5 and U.S. Patent No. 5,522,841 to Roby et al.), none of these publications discloses incorporating polymerizable groups on the polymers so that the polymers can be further polymerized. Accordingly, none of these polymers can be used in the same manner as the macromers in U.S. Patent No. 5,410,016 to Hubbell et al.

10           Sealing or plugging holes in lung tissue is inherently more difficult than sealing other types of tissue because the tissue is constantly expanded and contracted during normal respiration. It would be advantageous to provide macromers which can be rapidly polymerized *in vivo* to form hydrogels which are more elastic than conventional hydrogels, for  
15           example, for use in sealing lung tissue.

          It is therefore an object of the present invention to provide biodegradable, biocompatible macromers that can be rapidly polymerized *in vivo* to form hydrogels which are more elastic than conventional hydrogels.

20           It is a further object of the present invention to provide a macromer solution which can be administered during surgery or outpatient procedures and polymerized as a tissue adhesive, cell encapsulating medium, tissue sealant, wound dressing or drug delivery device.

          It is a still further object of the present invention to provide a  
25           macromer solution which can be polymerized *in vivo* on a surface to be coated in a very short time frame to form conformal coating layers.

### Summary of the Invention

          Biocompatible, biodegradable, polymerizable and at least substantially water-soluble macromers and methods of preparation and use  
30           thereof are disclosed. The macromers are block copolymers that include at least one water-soluble block, at least one biodegradable block, and at least

one polymerizable group. At least one of the biodegradable blocks comprises a linkage based on a carbonate or dioxanone group, and the macromers can contain other degradable linkages or groups in addition to carbonate or dioxanone.

5           The carbonate and dioxanone linkages impart more elasticity to the polymer and degrade at a different rate than hydroxy acid linkages. Carbonate linkages can also increase macromer viscosity, at a given concentration, without requiring increased molecular weight of the nondegradable components of the macromer. The macromers can also  
10       include poly(hydroxy acid) linkages which degrade by hydrolysis into relatively non-toxic hydroxy acid residues, or other biodegradable blocks such as polycaprolactones, polyorthoesters, polyanhydrides, and polypeptides. The degradation time of the polymers can be controlled, for example, by selecting the types and proportion of the biodegradable  
15       blocks.

          The polymerizable groups can be polymerized by either free radical (homolytic) processes or by heterolytic processes (such as cationic polymerization). Preferably, the groups are polymerized photochemically. The macromer can be polymerized in the presence of prophylactic,  
20       therapeutic or diagnostic agents, for delivery of the incorporated agents in a controlled manner as the resulting polymer degrades. The macromers are useful for delivering hydrophobic, hydrophilic and/or labile materials. They can be particularly useful for delivery of hydrophobic materials.

          The macromers can be polymerized in an interfacial manner to  
25       form ultrathin coatings which are intimately adhered to the coated surface, or in a bulk manner to form relatively thick coatings which may or may not be intimately adhered to the coated surface. Alternatively, the two methods can be combined to provide a relatively thick coating which is intimately adhered to the surface. Each of these methods is advantageous  
30       for certain applications.

### Brief Description of the Figures

Figure 1 is a graph of the elastic strength (seal pressure, mm Hg) over time (hr) of five different sealant materials: 10% 35K T, 20% 35K T, 10% 20K TL, 10% 20 K TL, and 20% 35K TL. K is defined as 100  
 5 Daltons (weight average molecular weight, T is trimethylene carbonate (TMC), L is lactide, and TL is a copolymer of TMC and lactide.

Figures 2A and 2B are graphs of the degradation (% mass loss) over time (days) for 20K T (Figure 2A) and 35K T (Figure 2B) for subcutaneous polymeric implants in rats.

10 Figure 3 shows the stress vs. strain curve of a compliant sealant formed by photopolymerization of a poly(ethylene glycol)-oligotrimethylene carbonate copolymer end capped with acrylate ester.

### Detailed Description of the Invention

#### Definitions

15 As used herein, the term "sealant" refers to a material which decreases or prevents the migration of fluid from or into a surface such as a tissue surface. Sealants are typically formed by the application of precursor molecules to a tissue followed by local polymerization. The same materials may also be used to adhere materials together, either when  
 20 applied between them and polymerized, or when used to jointly embed materials.

As used herein, the term "biocompatibility," in the context of biologically-related uses, refers to the absence of stimulation of a severe, long-lived or escalating biological response to an implant or coating, and  
 25 is distinguished from a mild, transient inflammation which typically accompanies surgery or implantation of foreign objects into a living organism.

As used herein the term "biodegradability" refers to the disintegration, which is preferably predictable, of an implant into small

entities which will be metabolized or excreted, under the conditions normally present in a living tissue.

The properties of the particular coating or barrier materials disclosed herein are referred to as "materials properties", and include:

5 the "Young's modulus" (of elasticity) which is the limiting modulus of elasticity extrapolated to zero strain;

the "elastic modulus" which is any modulus of elasticity, not limited to Young's modulus, and may include "secant modulus" and other descriptors of non-linear regions of the stress-strain curve;

10 the "bulk" or "compressive" modulus which is used in its usual sense of ratio of stress to a designated compressive strain;

the "elongation at failure" which is the relative strain or extension of a test specimen at which any irreversible or hysteresis-inducing change occurs in the specimen; and

15 the "elongation at break" or "elongation at rupture" which is the relative strain (extension) of a test specimen at which mechanical rupture occurs.

The term "compliance" as used herein is used in a general sense, and refers for example to the ability of an implant to closely match the physiological and mechanical properties of tissues at the implant site, except when "compliance" is used in a specific technical sense as the reciprocal of a modulus.

20 As applied to a relatively thin, flat material such as a tissue or a layer of sealant, "normalized compliance" (NC) is defined herein as the strain, (i.e., the elongation or compression per unit length of a specimen), divided by the applied force per unit cross-sectional area, further divided by the thickness of the specimen. Hence, for a sample having a width  $w$  (for example, the width of the clamps of the testing apparatus), and a thickness  $t$ , when an applied force  $F$  produces a strain  $S$ , then the

30 compliance  $C$  is

6

$$C = \frac{S}{F/wt} = \frac{S \cdot wt}{F}$$

and the normalized compliance is

$$NC = \frac{C}{t} = \frac{S}{F/w} = \frac{Sw}{F}$$

*i.e.*, the strain in the sample divided by the force per unit width applied to the sample. The normalized compliance allows direct comparison of the forces required to deform the tissue versus a coating on the tissue, without regard to the relative thicknesses of these materials.

5           The normalized compliance ratio (abbreviated NCR) is defined as the value of the normalized compliance of the tissue or other substrate divided by the normalized compliance of the sealant material. When both measurements are conducted on strips of the same width and at the same force, the NCR is simply the ratio of the strains at a particular force. A  
10 low NCR (less than 1) is obtained when the sealant material is easier to deform than the tissue, while a high NCR (greater than 1) is obtained when the tissue is easier to deform than the sealing material.

As used herein, the term "elastomer" refers to a polymeric material which at room temperature is capable of repeatedly recovering in size and  
15 shape after removal of a deforming force. In some embodiments, an elastomer is a material which can be repeatedly stretched to twice its original length and will repeatedly return to its approximate length on release of the stress.

The phrase "elastomeric materials" is a phrase which has been used  
20 in the literature. There are many publications describing structure-property relationships of elastomers and other deformable materials. Lower elastic modulus and, frequently, an increased reversible elongation to break or fracture, are found when any of the following occur:

1. The distance between nodes or junctions or more crystalline  
25 ("hard") segments increases.

2. The crosslink density decreases. This may be controlled by amount of crosslinker, nature of crosslinker, and degree of cure, as well as by segment length of either the crosslinked species or the crosslinking species, where different.

5           3. For a material at equilibrium with a continuous phase, an increase in the plasticization of the elastomer by the continuous phase. For applications wherein the continuous phase is water, more particularly physiological saline, increasing hydrophilicity tends to increase compliance.

10           In order to seal fluid leaks in tissue, the sealing material must remain firmly bonded to the tissue during motions required of the tissue during the healing process. For tissues and organs which cannot be immobilized, such as the lung, an effective sealing material is both tightly-adherent and compliant, having materials properties similar to those of the  
15           tissue. Examples of compliant adherent materials and methods for their construction and use are provided.

          In one embodiment, one or more initiators are applied to a surface to form an absorbed layer. "Absorbed" is used herein to encompass both "absorbed" and "adsorbed". A solution of polymerizable molecules,  
20           referred to herein as "monomers", is then applied.

### **Methods**

          In one embodiment, one or more initiators or components of an initiation system are applied directly to the surface, and the unabsorbed  
25           excess is optionally removed by washing or blotting. The initiator solution may further contain one or more polymerizable monomers, and other useful formulating ingredients, including accelerators, co-initiators, sensitizers, and co-monomers. Then a liquid containing polymerizable monomers in combination with one or more initiators or components of an  
30           initiation system, which may be the same as or different from that absorbed in the first step, is applied. The system, if not self-polymerizing,

is then stimulated to polymerize, for example by application of an appropriate wavelength of light.

The priming and monomer-application steps can also be combined. For example, if excess initiator is not removed before monomer addition, then subsequent application of monomer will result in mixture of initiator into the monomer layer. Similarly, if the monomer layer contains an initiator with a high affinity for the surface, then it is possible to apply a monomer layer containing initiator, and wait an appropriate time to allow preferential absorption of the initiator to the surface, to achieve the same effect.

All of these methods may collectively be described as application of the monomer in an "initiating-incorporating manner", encompassing any means of application and mixing which results in both an absorbed layer of initiator, and a layer of monomer incorporating an initiator, being present on a surface to be coated.

The initiators may be chemical, photochemical, or a combination thereof. With non-photochemical systems, a reductant component and an oxidant component may be present in the two parts of the solution, i.e., in the priming layer and the coating layer.

Alternatively, a two-step process can be used to form polymers, especially bioabsorbable hydrogels on tissue. In the first step the tissue is treated with an initiator or a part of an initiator system for the polymerization of olefinic (e.g. acrylic) or other functional monomers, optionally with monomer in the priming solution. This provides an activated tissue surface. In the second step, monomer(s) and, if appropriate, the remainder of an initiator system, are together placed in contact with the activated tissue, resulting in polymerization on the tissue. An example of such a system is the combination of a peroxygen compound in one part, and a reactive ion, such as a transition metal, in another.

This process of spontaneous polymerization does not require the use of a separate energy source. Moreover, since the process of polymerization is initiated when part one contacts part two, there are no "pot life" issues due to initiation of polymerization. If desired, part one or  
5 part two can contain dyes or other means for visualizing the hydrogel coating.

An example of a system that can be used in this method is the spontaneous "contact" initiator systems such as those found in two part "acrylic structural adhesives". All components of the materials used as  
10 described herein, however, must display biocompatibility as well as the ability to spontaneously polymerize on tissue. The use of tributyl borane for this purpose is illustrated here.

These systems can markedly simplify the delivery of gel to tissue, especially in areas hard to reach or hold for a photochemical system. The  
15 delivery system can be much simpler. Moreover, it has been discovered that a two-part chemical system such as a redox system and especially one based on peroxygen, can be used to chemically enhance the curing of a photochemical system, thereby combining the control of a photochemical system with the ability of a chemical system to overcome colored  
20 impurities, such as blood.

### **Polymers**

Water-soluble, biocompatible, biodegradable macromers and methods of preparation and use thereof, are disclosed. The macromers  
25 include at least one water-soluble block, at least one biodegradable block, and at least one polymerizable group. At least one biodegradable block contains a carbonate or dioxanone group. To obtain a biodegradable material after polymerization, each polymerizable group must be separated from any other polymerizable group on the macromer by at least one  
30 biodegradable linkage or group.

At least a portion of the macromers will contain more than one reactive group and thereby be effective as crosslinkers, so that the

macromers can be crosslinked to form a gel. The minimal proportion required will vary with the nature of the macromer and its concentration in solution, and the proportion of crosslinker in the macromer solution can be as high as 100% of the macromer solution.

5           For example, the macromers include at least 1.02 polymerizable groups on average, and, more preferably, the macromers each include two or more polymerizable groups on average.

          Since in the preferred homolytic (free radical) polymerization reactions each polymerizable group will polymerize into a chain,  
10       crosslinked hydrogels can be produced using only slightly more than one reactive group per macromer (i.e., about 1.02 polymerizable groups on average). However, higher percentages are preferable, and excellent gels can be obtained in polymer mixtures in which most or all of the molecules have two or more reactive double bonds. Poloxamines, an example of a  
15       water-soluble block, have four arms and thus may readily be modified to include four polymerizable groups.

          As used herein, a "biocompatible" material is one which stimulates only a mild, often transient, implantation response, as opposed to a severe or escalating response.

20           As used herein, a "biodegradable" material is one which decomposes under normal *in vivo* physiological conditions into components which can be metabolized or excreted.

          As used herein, a "block" is a region of a copolymer differing in subunit composition from neighboring regions. Blocks will generally  
25       contain multiple subunits, up to about one thousand subunits or less for non-degradable materials, and without an upper limit for degradable materials. In the lower limit, the size of a block depends on its function; the minimum size is that which is sufficient to allow the function to be performed. In the case of a block conferring water-solubility on the  
30       macromer, this will be typically 400 daltons or more, preferably 600 daltons or more, more preferably at least 1000 daltons, and most preferably in the range of 2000 to 40,000 daltons. For degradable

linkages, the minimum block size is a single linkage of the appropriate degradability for the function. More preferably, the block size is two to forty groups; most preferably, three to twenty. The reactive groups may be considered as a block for some purposes; the typical number of units in  
5 such a block is one, but may be two to five.

As used herein, a carbonate is a functional group with the structure  $-O-C(O)-O-$ . The carbonate starting material can be cyclic, such as trimethylene carbonate (TMC), or can be linear, such as dimethylcarbonate ( $CH_3O-C(O)-OCH_3$ ). After incorporation into the polymerizable  
10 macromer, the carbonate will be present at least in part as  $R-O-C(=O)-O-R'$ , where R and R' are other components of the macromer.

As used herein, a dioxanone is a repeating unit with the structure  $-O-C(O)-R-O-$ , where R is a straight, branched or cyclic alkyl group. An example of a cyclic dioxanone is 1,4-dioxan-2-one. 1,4-dioxan-2-one is a  
15 preferred dioxanone.

As used herein, a hydrogel is a substance formed when an organic polymer (natural or synthetic) is cross-linked via covalent, ionic, or hydrogen bonds to create a three-dimensional open-lattice structure which entraps water molecules to form a gel.

As used herein, "water-soluble" is defined as a solubility of at least  
20 one gram/liter in an aqueous solution at a temperature in the range of about 0° C and 50°C. Aqueous solutions can include small amounts of water-soluble organic solvents, such as dimethylsulfoxide, dimethylformamide, alcohols, acetone, and/or glymes.

### 25 **Types of Block Copolymers**

In general terms, the macromers are block co-polymers that comprise a biodegradable block, a water-soluble block, and at least one polymerizable group. Preferably, the macromers comprise at least 1.02 polymerizable groups on average, and, more preferably, include at least  
30 two polymerizable groups per macromer, on average. Average numbers of polymerizable groups can be obtained, for example, by blending macromers with different amounts of polymerizable groups.

The individual polymeric blocks can be arranged to form different types of block copolymers, including di-block, tri-block, and multi-block copolymers. The polymerizable blocks can be attached directly to biodegradable blocks or indirectly via water-soluble nondegradable blocks, and are preferably attached so that the polymerizable groups are separated from each other by a biodegradable block. For example, if the macromer contains a water-soluble block coupled to a biodegradable block, one polymerizable group may be attached to the water-soluble block and another attached to the biodegradable block. Preferably, both polymerizable groups would be linked to the water-soluble block by at least one degradable linkage.

The di-block copolymers include a water-soluble block linked to a biodegradable block, with one or both ends capped with a polymerizable group. The tri-block copolymers can include a central water-soluble block and outside biodegradable blocks, with one or both ends capped with a polymerizable group. Alternatively, the central block can be a biodegradable block, and the outer blocks can be water-soluble. The multiblock copolymers can include one or more of the water-soluble blocks and biocompatible blocks coupled together in a linear fashion. Alternatively, the multiblock copolymers can be brush, comb, dendritic or star copolymers. If the backbone is formed of a water-soluble block, at least one of the branches or grafts attached to the backbone is a biodegradable block. Alternatively, if the backbone is formed of a biodegradable block, at least one of the branches or grafts attached to the backbone is a water-soluble block, unless the biodegradable block is also water-soluble. In another embodiment, a multifunctional compound, such as a polyol, can be coupled to multiple polymeric blocks, at least one of which is water-soluble and at least one of which is biodegradable.

In general, any formulation of the macromer which is intended to be biodegradable must be constructed so that each polymerizable group is separated from each other polymerizable group by one or more linkages

which are biodegradable. Non-biodegradable materials are not subject to this constraint.

Those skilled in the art will recognize that the individual polymeric blocks may have uniform compositions, or may have a range of molecular weights, and may be combinations of relatively short chains or individual species which confer specifically desired properties on the final hydrogel, while retaining the required characteristics of the macromer. The lengths of oligomers referred to herein may vary from single units (in the biodegradable portions) to many, subject to the constraint of preserving the overall water-solubility of the macromer.

In the discussion below and the examples, macromers are often designated by a code of the form xxKZn. xxK represents the molecular weight of the backbone polymer, which is polyethylene glycol ("PEG") unless otherwise stated, in thousands of Daltons. Z designates the biodegradable linkage, using a code wherein where L is for lactic acid, G is for glycolic acid, D is for dioxanone, C is for caprolactone, T is for trimethylene carbonate, and n is the average number of degradable groups in the block. The molecules are terminated with acrylic ester groups, unless otherwise stated. This is sometimes also indicated by the suffix A2.

While the preferred biodegradable groups (in addition to carbonate or dioxanone) are hydroxy acids, orthoesters, anhydrides, or other synthetic or semisynthetic degradable linkages, natural materials may be used in the biodegradable sections when their degree of degradability is sufficient for the intended use of the macromer. Such biodegradable groups may comprise natural or unnatural amino acids, carbohydrate residues, and other natural linkages. Biodegradation time will be controlled by the local availability of enzymes hydrolyzing such linkages. The availability of such enzymes may be ascertained from the art or by routine experimentation.

**Water soluble regions.**

Suitable water-soluble polymeric blocks include those prepared from poly(ethylene glycol), poly(ethylene oxide), partially or fully hydrolyzed poly(vinyl alcohol), poly(vinylpyrrolidone),  
5 poly(ethyloxazoline), poly(ethylene oxide)-co-poly(propylene oxide) block copolymers (poloxamers and meroxapols), poloxamines, carboxymethyl cellulose, hydroxyalkylated celluloses such as hydroxyethyl cellulose and methylhydroxypropyl cellulose, polypeptides, polynucleotides, polysaccharides or carbohydrates such as Ficoll® polysucrose, hyaluronic  
10 acid, dextran, heparan sulfate, chondroitin sulfate, heparin, or alginate, and proteins such as gelatin, collagen, albumin, or ovalbumin. Preferably, the water-soluble polymeric blocks are made from poly(ethylene glycol) or poly(ethylene oxide).

The soluble polymer blocks may be intrinsically biodegradable or  
15 may be poorly biodegradable or effectively non-biodegradable in the body. In the latter two cases, the soluble blocks should be of sufficiently low molecular weight to allow excretion. The maximum molecular weight to allow excretion in human beings (or other species in which use is intended) will vary with polymer type, but will often be about 40,000  
20 daltons or below. Water-soluble natural polymers and synthetic equivalents or derivatives, including polypeptides, polynucleotides, and degradable polysaccharides, can be used.

The water-soluble blocks can be a single block with a molecular weight of at least 600, preferably 2000 or more, and more preferably at  
25 least 3000 Daltons. Alternatively, the water-soluble blocks can be two or more water-soluble blocks which are joined by other groups. Such joining groups can include biodegradable linkages, polymerizable linkages, or both. For example, an unsaturated dicarboxylic acid, such as maleic, fumaric, or aconitic acid, can be esterified with degradable groups as  
30 described below, and such linking groups can be conjugated at one or both ends with hydrophilic groups such as polyethylene glycols. In another embodiment, two or more PEG molecules can be joined by biodegradable

linkages including carbonate linkages, and subsequently be end-capped with polymerizable groups.

### **Biodegradable Blocks.**

The biodegradable blocks are preferably hydrolyzable under *in vivo* conditions. At least one biodegradable region is a carbonate or dioxanone linkage. Additional biodegradable polymeric blocks can include polymers and oligomers of hydroxy acids or other biologically degradable polymers that yield materials that are non-toxic or present as normal metabolites in the body. Preferred poly(hydroxy acid)s are poly(glycolic acid), poly(DL-lactic acid) and poly(L-lactic acid). Other useful materials include poly(amino acids), poly(anhydrides), poly(orthoesters), and poly(phosphoesters). Polylactones such as poly(epsilon-caprolactone), poly(delta-valerolactone), poly(gamma-butyrolactone) and poly(beta-hydroxybutyrate), for example, are also useful.

Biodegradable regions can be constructed from monomers, oligomers or polymers using linkages susceptible to biodegradation, such as ester, peptide, anhydride, orthoester, and phosphoester bonds.

By varying the total amount of biodegradable groups, and selecting the ratio between the number of carbonate or dioxanone linkages (which are relatively slow to hydrolyze) and of lower hydroxy acid linkages (especially glycolide or lactide, which hydrolyze relatively rapidly), the degradation time of hydrogels formed from the macromers can be controlled.

### **Carbonates and Dioxanones**

Any carbonate can be used to make the macromers. Preferred carbonates are aliphatic carbonates, for maximum biocompatibility. For example, trimethylene carbonate and dimethyl carbonate are examples of aliphatic carbonates. Lower dialkyl carbonates are joined to backbone polymers by removal by distillation of alcohols formed by equilibration of dialkyl carbonates with hydroxyl groups of the polymer.

More preferred carbonates are the cyclic carbonates, which can react with hydroxy-terminated polymers without release of water. Suitable

cyclic carbonates include ethylene carbonate (1,3-dioxolan-2-one), propylene carbonate (4-methyl -1,3-dioxolan-2-one), trimethylene carbonate (1,3-dioxan-2-one) and tetramethylene carbonate (1,3-dioxepan-2-one). Under some reaction conditions, it is possible that orthocarboxonates may react to give carbonates, or that carbonates may react with polyols via orthocarbonate intermediates, as described in Timberlake et al, U. S. 4,330,481. Thus, certain orthocarboxonates, particularly dicyclic orthocarboxonates, can be suitable starting materials for forming the carbonate-linked macromers.

Alternatively, suitable diols or polyols, including backbone polymers, can be activated with phosgene to form chloroformates, as is described in the art, and these active compounds can be mixed with backbone polymers containing suitable groups, such as hydroxyl groups, to form macromers containing carbonate linkages.

All of these materials are "carbonates" as used herein.

Suitable dioxanones include dioxanone (p-dioxanone; 1,4-dioxan-2-one; 2-keto-1,4-dioxane), and the closely related materials 1,4-dioxolan-2-one, 1,4-dioxepan-2-one and 1,5-dioxepan-2-one. Lower alkyl, for example C1-C4 alkyl, derivatives of these compounds are also contemplated, such as 2-methyl p-dioxanone (cyclic O-hydroxyethyl ether of lactic acid).

### **Polymerizable Groups.**

The term "polymerizable group" is defined as a reactive functional group that has the capacity to form additional covalent bonds resulting in macromer interlinking. Polymerizable groups specifically include groups capable of polymerizing via free radical polymerization and groups capable of polymerizing via cationic or heterolytic polymerization. Suitable groups include, but are not limited to, ethylenically or acetylenically unsaturated groups, isocyanates, epoxides (oxiranes), sulfhydryls, succinimides, maleimides, amines, imines, amides, carboxylic acids, sulfonic acids and phosphate groups. (Aliphatic hydroxy groups are not considered to be reactive groups for the chemistry disclosed herein, except

in formulations which also contain groups capable of covalent crosslinking with such hydroxyls.) Ethylenically unsaturated groups include vinyl groups such as vinyl ethers, N-vinyl amides, allyl groups, unsaturated monocarboxylic acids, unsaturated dicarboxylic acids, and unsaturated

5 tricarboxylic acids. Unsaturated monocarboxylic acids include acrylic acid, methacrylic acid and crotonic acid. Unsaturated dicarboxylic acids include maleic, fumaric, itaconic, mesaconic or citraconic acid.

Unsaturated tricarboxylic acids include aconitic acid. Polymerizable groups may also be derivatives of such materials, such as acrylamide,

10 N-isopropylacrylamide, hydroxyethylacrylate, hydroxyethylmethacrylate, and analogous vinyl and allyl compounds. Reactive group forming compounds will preferably be available in a stable activated form, to allow simple incorporation into the macromer. Examples of such materials are (meth)acrylyl chloride, acrylic anhydride, and allyl glycidyl ether. The

15 polymerizable groups are preferably located at one or more ends of the macromer. In a less preferred embodiment, the polymerizable groups can be located within the macromer.

Polymerization is initiated by any convenient reaction, including photopolymerization, chemical or thermal free-radical polymerization,

20 redox reactions, cationic polymerization, and chemical reaction of active groups (such as isocyanates, for example.) Polymerization is preferably initiated using photoinitiators. Photoinitiators that generate a free radical or a cation on exposure to UV light are well known to those of skill in the art. Free-radicals can also be formed in a relatively mild manner from

25 photon absorption of certain dyes and chemical compounds. The polymerizable groups are preferably polymerizable by free radical polymerization. The preferred polymerizable groups are acrylates, diacrylates, oligoacrylates, methacrylates, dimethacrylates, oligomethacrylates, cinnamates, dicinnamates, oligocinnamates, and other

30 biologically acceptable photopolymerizable groups.

These groups can be polymerized using photoinitiators that generate free radicals upon exposure to light, including UV (ultraviolet) and IR

(infrared) light, preferably long-wavelength ultraviolet light (LWUV) or visible light. LWUV and visible light are preferred because they cause less damage to tissue and other biological materials than short-wave UV light. Useful photoinitiators are those which can be used to initiate  
5 polymerization of the macromers without cytotoxicity and within a short time frame, minutes at most and most preferably seconds.

Exposure of dyes, preferably in combination with co-catalysts such as amine, to light, preferably visible or LWUV light, can generate free radicals. Light absorption by the dye causes the dye to assume a triplet  
10 state, and the triplet state subsequently reacts with the amine to form a free radical which initiates polymerization, either directly or via a suitable electron transfer reagent or co-catalyst, such as an amine. Polymerization can be initiated by irradiation with light at a wavelength of between about 200-1200 nm, most preferably in the long wavelength ultraviolet range or  
15 visible range, 320 nm or higher, and most preferably between about 365 and 550 nm.

Numerous dyes can be used for photopolymerization. Suitable dyes are well known to those of skill in the art. Preferred dyes include erythrosin, phloxime, rose bengal, thionine, camphorquinone, ethyl eosin,  
20 eosin, methylene blue, riboflavin, 2,2-dimethyl-2-phenylacetophenone, 2-methoxy-2-phenylacetophenone, 2,2-dimethoxy-2-phenyl acetophenone, other acetophenone derivatives, and camphorquinone. Suitable cocatalysts include amines such as N-methyl diethanolamine, N,N-dimethyl benzylamine, triethanol amine, triethylamine, dibenzyl amine,  
25 N-benzylethanolamine, N-isopropyl benzylamine. Triethanolamine is a preferred cocatalyst.

Suitable chemical, thermal and redox systems may initiate the polymerization of unsaturated groups by generation of free radicals in the initiator molecules, followed by transfer of these free radicals to the  
30 unsaturated groups to initiate a chain reaction. Peroxides and other peroxygen compounds are well-known in this regard, and may be considered as chemical or thermal initiators. Azobisbutyronitrile is a

chemical initiator. A combination of a transition metal, especially iron, with a peroxygen and preferably a stabilizing agent such as glucuronic acid allows generation of free radicals to initiate polymerization by a cycling redox reaction.

5 Combinations of chemical or redox systems with photoinitiated systems have been demonstrated to be effective in WO 96/29370, and are a preferred initiation system for many applications of the macromers of the present invention.

It is also possible to use the macromers with other types of linking  
10 reactions. For example, a macromer could be constructed with amine termination, with the amine considered as an active group; and another macromer could be constructed with isocyanate termination, with the isocyanate as the active group. On mixing, the materials will spontaneously react to form a gel. Alternatively, an isocyanate-terminated  
15 macromer could be polymerized and crosslinked with a mixture of diamines and triamines. Such a reaction is more difficult to control than a photoinitiated reaction, but could be preferred for high volume extracorporeal production of gels for implantation, perhaps as drug delivery systems. Other pairs of reactants include maleimides with amines  
20 or sulfhydryls, or oxiranes with amines, sulfhydryls or hydroxyls.

#### Preferred Macromers

Preferably, the macromers contain between about 0.3% and 20% by weight of carbonate residues or dioxanone residues, more preferably, between about 0.5% and 15% carbonate or dioxanone residues, and most  
25 preferably, about 1% to 5% carbonate or dioxanone residues. In those embodiments where hydroxy acid residues are desired, the macromer contains between about 0.1 and 10 residues per residue of carbonate or dioxanone, more preferably between about 0.2 and 5, and most preferably one or more such residue per macromer.

30 In a preferred embodiment, the macromer includes a core, an extension on each end of the core, and an end cap on each extension. The core is a hydrophilic polymer or oligomer; each extension is a

biodegradable oligomer comprising one or more carbonate or dioxanone linkage; and each end cap comprises one or more functional groups capable of cross-linking the macromers. In a particularly preferred embodiment, the core includes hydrophilic poly(ethylene glycol) oligomers with a molecular weight between about 400 and 40,000 Da; each extension includes 1 to 10 residues selected from carbonate and dioxanone, and optionally further included between one and five hydroxyacid residues, preferably alpha-hydroxy acid residues; wherein the total of all residues in the extensions is sufficiently small to preserve water-solubility of the macromer, being typically less than about 20% of the weight of the macromer, more preferably 10% or less.

Preferably, each end cap includes a polymerizable group. The preferred groups are free-radical (homolytically) polymerizable. More preferably, they are ethylenically-unsaturated (i.e., containing carbon-carbon double bonds), with a preferred molecular weight between about 50 and 300 Da, which are capable of cross-linking and/or polymerizing the macromers. A preferred embodiment incorporates a core consisting of poly(ethylene glycol) oligomers of molecular weight about 25,000 Da; extensions including polycarbonate or poly(dioxanone) oligomers with a molecular weight of about 200 to 1000 D, alone or in combination with extensions formed of hydroxy acid oligomers; and end caps consisting of acrylate moieties (which are about 55 Da molecular weight).

### Macromer Synthesis

The macromers can be synthesized using means well known to those of skill in the art. General synthetic methods are found in the literature, for example in U.S. Patent No. 5,410,016 to Hubbell et al., U.S. Patent No. 4,243,775 to Rosensaft et al., and U.S. Patent No. 4,526,938 to Churchill et al.

For example, a polyethylene glycol backbone can be reacted with trimethylene carbonate (TMC) or a similar carbonate in the presence of a Lewis acid catalyst, such as stannous octoate, to form a TMC-polyethylene

glycol terpolymer. The TMC-PEG polymer may optionally be further derivatized with additional degradable groups, such as lactate groups. The terminal hydroxyl groups can then be reacted with acryloyl chloride in the presence of a tertiary amine to end-cap the polymer with acrylate end-groups. Similar coupling chemistry can be employed for macromers containing other water-soluble blocks, biodegradable blocks, and polymerizable groups, particularly those containing hydroxyl groups.

When polyethylene glycol is reacted with TMC and a hydroxy acid in the presence of an acidic catalyst, the reaction can be either simultaneous or sequential. As shown in the examples below, the simultaneous reaction will produce an at least partially random copolymer of the three components. Sequential addition of a hydroxy acid after reaction of the PEG with the TMC will tend to produce an inner copolymer of TMC and one or more PEGs, which will statistically contain more than one PEG residue linked by linkages derived from TMC, with hydroxy acid largely at the ends of the (TMC, PEG) region. There is a tendency for TM and other carbonate groups to re-arrange by "back-biting" during synthesis, which is why multiple PEG molecules can become incorporated in the same macromer. When the hydroxy acid contains a secondary hydroxyl, as in lactic acid, then the tendency towards rearrangement is reduced.

In principle, the degradable blocks or regions could be separately synthesized and then coupled to the backbone regions. In practice, this more complex reaction does not appear to be required to obtain useful materials.

### Sequential Addition

In a preferred embodiment, sequential addition of biodegradable groups to a carbonate-containing macromer can be used to enhance biodegradability of the macromer after capping with reactive end groups.

Upon reaction of, for example, trimethylene carbonate (TMC) with polyethylene glycol (PEG), the TMC linkages in the resulting copolymers have been shown to form end linked species of PEG, resulting in

segmented copolymers, i.e. PEG units coupled by one or more adjacent TMC linkages. The length of the TMC segments can vary, and is believed to exhibit a statistical distribution. Coupling may also be accomplished via the carbonate subunit of TMC. These segmented PEG/TMC copolymers form as a result of transesterification reactions involving the carbonate linkages of the TMC segments during the TMC polymerization process when a PEG diol is used as an initiator. Similar behavior is expected if other polyalkylene glycol initiators were used. The end-linking may begin during the reaction of the TMC with the PEG, and completion of the end linking and attainment of equilibrium is observable by a cessation of increase of the viscosity of the solution.

If the product of this first reaction step is then reacted with a reactive end-capping material, such as acryloyl chloride, a significant percentage of the macromer end groups can be PEG hydroxyls, resulting in the attachment of the reactive groups directly to one end of a non-biodegradable PEG molecule. Such a reaction of the PEG/TMC segmented copolymers can be prevented by adding additional segments of other hydrolyzable co-monomers (e.g. lactate, glycolate, 1,4-dioxanone, dioxepanone, caprolactone) on either end of the PEG/TMC segmented copolymer. Some scrambling of the comonomer segments with the PEG/TMC prepolymer is expected, but this can be minimized by using proper reaction conditions. The basic PEG/TMC segmented copolymer or the further reacted PEG/TMC/comonomer segmented terpolymer is then further reacted to form crosslinkable macromers by affixing reactive end groups (such as acrylates) to provide a macromer with reactive functionality. Subsequent reaction of the end groups in an aqueous environment results in a bioabsorbable hydrogel. Similar segmented structures would be expected if another polyalkylene glycol (PAG) were used, for example a poloxamer.

The copolymers and macromers can have tailorable solubility and solution viscosity properties. The hydrogels can have tailorable modulus and degradation rate. For a given solution concentration in water, the

viscosity is affected by the degree of end linking, the length of the TMC (and other hydrophobic species) segments, and the molecular weight of the starting PAG. The modulus of the hydrogel is affected by the molecular weight between crosslinks. The hydrogel degradation rate can be modified by adding a second, more easily hydrolyzed comonomer (e.g. lactate, glycolate, 1,4-dioxanone) as a segment on the ends of the basic PAG/TMC copolymer prior to adding the crosslinkable end group to form the macromer.

Some of these structures described herein are depicted below.

PEG, lactate and acrylate units are used solely for purposes of illustration.

#### SOME BASIC STRUCTURES:

$(\text{CH}_2\text{-CH}_2\text{-O})_x = \text{PEG repeat unit} = (\text{PEG})_x$

$(\text{CO}\text{-(CH}_2)_3\text{-O})_y = \text{TMC repeat unit} = (\text{TMC})_y$

$(\text{CO}\text{-CH(CH}_3\text{)-O})_z = \text{Lactate repeat unit} = (\text{LA})_z$

$\text{-CO}\text{-CH=CH}_2 = \text{Acrylate end group} = \text{AA}$

#### SEGMENTED PEG/TMC COPOLYMER:

$\text{HO}\text{-(CO}\text{-(CH}_2)_3\text{-O)}_y\text{-}[(\text{CH}_2\text{-CH}_2\text{-O)}_x\text{-(CO}\text{-(CH}_2)_3\text{-O)}_y]_n\text{-H}$

or  $\text{HO}\text{-(TMC)}_y\text{-(PEG)}_x\text{-(TMC)}_y]_n\text{-H}$

#### SEGMENTED PEG/TMC/Lactate TERPOLYMER:

$\text{HO}\text{-(CH(CH}_3\text{)-CO)}_z\text{-O-(CO}\text{-(CH}_2)_3\text{-O)}_y\text{-}[(\text{CH}_2\text{-CH}_2\text{-O)}_x\text{-(CO}\text{-(CH}_2)_3\text{-O)}_y]_n\text{-(CO}\text{-CH(CH}_3\text{)-O)}_z\text{-H}$

or  $\text{HO}\text{-(LA)}_z\text{-(TMC)}_y\text{-(PEG)}_x\text{-(TMC)}_y]_n\text{-(LA)}_z\text{-H}$

#### SEGMENTED PEG/TMC MACROMER (acrylated):

$\text{CH}_2\text{=CH}\text{-CO}\text{-O-(CO}\text{-(CH}_2)_3\text{-O)}_y\text{-}[(\text{CH}_2\text{-CH}_2\text{-O)}_x\text{-(CO}\text{-(CH}_2)_3\text{-O)}_y]_n\text{-CO}\text{-CH=CH}_2$

H<sub>2</sub>

or  $\text{AA}\text{-(TMC)}_y\text{-(PEG)}_x\text{-(TMC)}_y]_n\text{-AA}$

SEGMENTED PEG/TMC/Lactate TERPOLYMER MACROMER(acrylated):5        Applications for the Macromers.Methods of Treatment

Generally, any medical condition which requires a coating or sealing layer may be treated by the methods described herein to produce a coating with better adherence. For example, lung tissue may be sealed  
 10 against air leakage after surgery using the priming technique. Likewise, wounds may be closed; leakage of blood, serum, urine, cerebrospinal fluid, air, mucus, tears, bowel contents or other bodily fluids may be stopped or minimized; barriers may be applied to prevent post-surgical adhesions, including those of the pelvis and abdomen, pericardium, spinal cord and  
 15 dura, tendon and tendon sheath. The technique may also be useful for treating exposed skin, in the repair or healing of incisions, abrasions, burns, inflammation, and other conditions requiring application of a coating to the outer surfaces of the body. The technique is also useful for applying coatings to other body surfaces, such as the interior or exterior of  
 20 hollow organs, including blood vessels. In particular, restenosis of blood vessels or other passages can be treated. The techniques can also be used for attaching cell-containing matrices, or cells, to tissues, such as meniscus or cartilage.

Sealing Leaks in Tissue

25        A preferred application of the polymers is in a method of sealing leaks, for example, leaks of gases and/or bodily fluids (such as blood, cerebrospinal fluid, urine and bile), in tissue such as lung, urethra, ureter, gastrointestinal tract, reproductive tract, liver, spleen, dura, and the spinal cord.

30        In thoracic surgery, uses include sealing of bronchopleural fistulas, reduction of mediastinal bleeding, sealing of esophageal anastomoses, and sealing of pulmonary staple or suture lines. In neurosurgery, uses include

dural repairs, microvascular surgery, and peripheral nerve repair. In general surgery, uses include bowel anastomoses, liver resection, biliary duct repair, pancreatic surgery, lymph node resection, reduction of seroma and hematoma formation, endoscopy-induced bleeding, plugging or sealing  
5 of trocar incisions, and repair in general trauma, especially in emergency procedures.

In plastic surgery, uses include skin grafts, burns, debridement of eschars, and blepharoplasties (eyelid repair). In otorhinolaryngology (ENT), uses include nasal packing, ossicular chain reconstruction, vocal  
10 cord reconstruction and nasal repair. In ophthalmology, uses include corneal laceration or ulceration, and retinal detachment. In orthopedic surgery, uses include tendon repair, bone repair, including filling of defects, and meniscus repairs. In gynecology/obstetrics, uses include treatment of myotomies, repair following adhesiolysis, and prevention of  
15 adhesions. In urology, sealing and repair of damaged ducts, and treatment after partial nephrectomy are potential uses. Sealing can also be of use in stopping diffuse bleeding in any of a variety of situations, including especially treatment of hemophiliacs. In dental surgery, uses include treatment of periodontal disease and repair after tooth extraction. Repair  
20 of incisions made for laparoscopy or other endoscopic procedures, and of other openings made for surgical purposes, are other uses. Additional uses include separation of tissues to prevent damage by rubbing during healing. Similar uses can be made in veterinary procedures. In each case, appropriate biologically active components may be included in the sealing  
25 or bonding materials.

The method involves priming the surface of the tissue with a polymerization initiator, applying a macromer solution that also contains one or more polymerization initiators to the surface of the tissue to be coated, and then polymerizing the macromer. Preferably, the  
30 polymerization initiator comprises a photoinitiator.

Applying the initiator to surface of the tissue before adding the macromer solution polymerizes the macromer at the interface between the

solution and the tissue surface. This "interfacial polymerization" provides excellent adherence of the resulting polymer to the tissue surface.

Providing an initiator in the macromer solution allows a relatively thick, for example 1 mm to 10 mm, layer of polymer to be formed on the tissue surface. Relatively thick polymer layers may be required to effectively seal some types of tissue, for example, lung tissue or dura, depending on the size of the leak.

An advantage of the macromers when prepared with at least one carbonate group is that during the synthesis of the macromer, short blocks of non-biodegradable but excretable polymer, such as polyethylene oxide chains of up to about 40,000 D, can become linked by carbonate groups so give higher molecular weights to the macromers while preserving the biodegradability to secretable products of the macromer. It is believed that the higher molecular weights increase the elasticity of the final hydrogel. This is an important and useful property when the polymer must be readily and repeatedly stretched, as in a sealant layer applied to lung tissue. High elasticity can also be provided by linking nondegradable blocks with other polyfunctional linkers, such as dicarboxylic acids. However, since the synthetic chemistry required to make such macromers can be more complex than the simple reactions required for carbonate-based linking, this method is less preferred.

#### **Prevention of Surgical Adhesions.**

Another preferred application is a method of reducing formation of adhesions after a surgical procedure in a patient. The method involves coating damaged tissue surfaces in a patient with an aqueous solution of a light-sensitive free-radical polymerization initiator and a macromer solution as described above. The coated tissue surfaces are exposed to light sufficient to polymerize the macromer. The light-sensitive free-radical polymerization initiator may be a single compound (e.g., 2,2-dimethoxy-2-phenyl acetophenone) or a combination of a dye and a cocatalyst (e.g., ethyl eosin or eosin Y, and triethanolamine).

**Controlled delivery of incorporated agents.**

Another preferred application involves locally applying an incorporated agent, such as a prophylactic, therapeutic or diagnostic agent, to tissue surfaces of a patient. The method includes the steps of mixing an agent to be incorporated with an aqueous solution including a suitable  
5 polymerization initiator, such as a light-sensitive free-radical polymerization initiator, and a macromer, to form a coating mixture. Tissue surfaces are coated with the coating mixture and the macromer is polymerized, for example, by exposure of the coating mixture to an  
10 effective amount of light of an appropriate wavelength.

Any of a variety of therapeutic, prophylactic or diagnostic agents can be delivered using these methods. Examples include synthetic and natural inorganic and organic compounds such as proteins (100 amino acid residues or more), peptides (less than 100 amino acid residues),  
15 carbohydrates, lipids, nucleic acid molecules, and small synthetic materials such as ethical drugs, having therapeutic, prophylactic or diagnostic activities. Nucleic acid molecules include genes, antisense molecules which bind to complementary DNA to inhibit transcription, aptamers, triple helix forming oligomers and ribozymes. The agents to be delivered  
20 can have a variety of biological activities. Diagnostic agents such as radiolabelled compounds, enzymatically labeled compounds, fluorescently labeled compounds, and other detectable agents can also be incorporated. Compounds with a wide range of molecular weights can be incorporated, for example, between 100 and 500,000 grams or more per mole.

25 Therapeutic or prophylactic compounds ("drugs") of particular interest are those whose efficacy in treatment of a localized medical condition is increased by local delivery of the compound at or near the site of the localized medical condition. Examples of classes of such drugs are those which inhibit the formation or re-formation of scars or adhesions;  
30 those which prevent unwanted proliferation of vascular tissue or other luminal tissue; and growth factors, cytokines, etc. which only needs to be effective locally.

Imaging agents which may be utilized include commercially available agents used in positron emission tomography (PET), computer assisted tomography (CAT), single photon emission computerized tomography, x-ray, fluoroscopy, and magnetic resonance imaging (MRI).

5        Examples of suitable materials for use as contrast agents in MRI include the gadolinium chelates currently available, such as diethylene triamine pentacetic acid (DTPA) and gadopentotate dimeglumine, as well as iron, magnesium, manganese, copper and chromium.

10        Examples of materials useful for CAT and x-rays include iodine based materials for intravenous administration, such as ionic monomers typified by diatrizoate and iothalamate, non-ionic monomers such as iopamidol, isohexol, and ioversol, non-ionic dimers, such as iotrol and iodixanol, and ionic dimers, for example, ioxagalte.

15        Hydrogels incorporating these agents can be detected using standard techniques available in the art and commercially available equipment.

20        The macromers are particularly useful for delivering hydrophilic and/or labile materials. Because the macromer is water-soluble, water can penetrate the polymer and dissolve or extract incorporated hydrophilic materials. Labile materials can be incorporated without exposure of the material to organic solvents which would destroy biological activity. Hydrophobic materials may also be incorporated, if the rate of dissolution of the hydrophobic material and/or the gel matrix is sufficiently rapid to release the material at a therapeutically-effective rate. In all cases, the polymerized hydrogel will tend to protect the therapeutic material from  
25        attack by biological activities of the subject, such as enzyme activity.

In a variation of the method for controlled drug delivery, the macromers are polymerized with incorporated

#### **Preferred Macromers**

30        Preferably, the macromers contain between about 0.3% and 20% by weight of carbonate residues or dioxanone residues, more preferably, between about 0.5% and 15% carbonate or dioxanone residues, and most preferably, about 1% to 5% carbonate or dioxanone residues. In those

embodiments where hydroxy acid residues are desired, the macromer contains between about 0.1 and 10 residues per residue of carbonate or dioxanone, more preferably between about 0.2 and 5, and most preferably one or more such residue per macromer.

5 In a preferred embodiment, the macromer includes a core, an extension on each end of the core, and an end cap on each extension. The core is a hydrophilic polymer or oligomer; each extension is a biodegradable oligomer comprising one or more carbonate or dioxanone linkage; and each end cap comprises one or more functional groups  
10 capable of cross-linking the macromers. In a particularly preferred embodiment, the core includes hydrophilic poly(ethylene glycol) oligomers with a molecular weight between about 400 and 40,000 Da; each extension includes 1 to 10 residues selected from carbonate and dioxanone, and optionally further included between one and five hydroxyacid residues,  
15 preferably alpha-hydroxy acid residues; wherein the total of all residues in the extensions is sufficiently small to preserve water-solubility of the macromer, being typically less than about 20% of the weight of the macromer, more preferably 10% or less.

Preferably, each end cap includes a polymerizable group. The  
20 preferred groups are free-radical (homolytically) polymerizable. More preferably, they are ethylenically-unsaturated (i.e., containing carbon-carbon double bonds), with a preferred molecular weight between about 50 and 300 Da, which are capable of cross-linking and/or polymerizing the macromers. A preferred embodiment incorporates a core  
25 consisting of poly(ethylene glycol) oligomers of molecular weight about 25,000 Da; extensions including polycarbonate or poly(dioxanone) oligomers with a molecular weight of about 200 to 1000 D, alone or in combination with extensions formed of hydroxy acid oligomers; and end caps consisting of acrylate moieties (which are about 55 Da molecular  
30 weight).

### **Tissue Adhesives.**

The macromers, and hydrogels formed therefrom, can also be used to adhere tissue surfaces in a patient. The macromer is mixed with a suitable polymerization initiator system, such as a photoinitiator or photoinitiator/amine mixture, to form an aqueous mixture. The mixture is applied to a tissue surface to which tissue adhesion is desired. The tissue surface is contacted with the tissue with which adhesion is desired, forming a tissue junction. The macromers are then polymerized at the tissue junction.

Such a technique can be used to hold surgically severed tissue in apposition during the healing process, thereby replacing or supplementing the use of sutures, staples, etc. In addition, such a gel may also be used to form a protective barrier.

### **Coating of Surfaces**

Surfaces to be coated include biologically-related surfaces of all kinds, and include the surface of drug delivery devices such as catheters or prosthetic implants. Any tissue or cell surface is contemplated, as well as the surface of a device to be used in the body or in contact with bodily fluids. A coating may be applied to the surface of any of these, in an amount effective to improve tenacity of adherence. Moreover, the technique may be used to adhere surfaces to each other. For example, wounds in living tissue may be bonded or sealed using this technique or preformed medical appliances may be bonded to tissue. Examples of such applications are grafts, such as vascular grafts; implants, such as heart valves, pacemakers, artificial corneas, and bone reinforcements; supporting materials, such as meshes used to seal or reconstruct openings; and other tissue-non-tissue interfaces. A particularly important class of tissue surfaces is those which are friable, and therefore will not support sutures well. Adherent coatings can seal the suture lines, support sutured areas against mechanical stress, or substitute entirely for sutures when mechanical stress is low. Examples of such situations include vascular

anastomosis, nerve repair, repair of the cornea or the cochlea, and repair of the lung, liver, kidney and spleen.

The priming technique can also be used on non-tissue surfaces in general, where useful bonds may be formed between similar or dissimilar substances, and solid or gel coatings are tightly adhered to surfaces. In particular, a pre-formed gel, or other fragile material, may be tightly adhered to a supporting material by this method.

The priming method is advantageous because it can be used to coat and or to bond together any of a wide variety of surfaces. These include all surfaces of the living body, and surfaces of medical devices, implants, wound dressings and other body-contacting artificial or natural surfaces. These include, but are not limited to, at least one surface selected from the following: a surface of the respiratory tract, the meninges, the synovial spaces of the body, the peritoneum, the pericardium, the synovia of the tendons and joints, the renal capsule and other serosae, the dermis and epidermis, the site of an anastomosis, a suture, a staple, a puncture, an incision, a laceration, or an apposition of tissue, a ureter or urethra, a bowel, the esophagus, the patella, a tendon or ligament, bone or cartilage, the stomach, the bile duct, the bladder, arteries and veins; and devices such as percutaneous catheters (e.g. central venous catheters), percutaneous cannulae (e.g. for ventricular assist devices), urinary catheters, percutaneous electrical wires, ostomy appliances, electrodes (surface and implanted), and implants including pacemakers, defibrillators. and tissue augmentations.

In a particularly preferred application of these macromers, an ultra thin coating is applied to the surface of a tissue, most preferably the inside surface of a blood vessel. Such coatings can be used to treat or prevent stenosis or restenosis of blood vessels. A polymerization initiator, preferably a photoinitiator, is applied to the surface of the tissue, allowed to stain the tissue, and, optionally, the excess photoinitiator is removed by dilution or rinsing. After the initiator has been applied to the tissue, the macromer solution is applied and the macromer is polymerized. As demonstrated below, this method is capable of creating a uniform polymeric coating of between about one and 300 microns in thickness, more preferably about ten to 200 microns, most preferably 20 to 80 microns, which does not evoke thrombosis during its residence at the site.

The surface of medical devices can be coated with the macromers using interfacial polymerization, bulk polymerization, or both, as discussed above. Coating layers applied using interfacial polymerization or a combination of interfacial and bulk polymerization typically adhere more strongly to the medical devices than those prepared using only bulk polymerization.

#### APPLICATION TECHNIQUES AND DEVICES

Both priming and polymer addition may be accomplished by simple dripping of material onto the surface to be coated. This can be accomplished using common devices such as a syringe, a pipet, or a hose, depending on scale. More uniform applications may be obtained using an applicator, such as a brush, a pad, a sponge, a cloth, or a spreading device such as a finger, a coating blade, a balloon, or a skimming device. These may further be used to rub the surface to improve penetration of the primer or the monomer, or to mix primer and monomer *in situ* on the surface. In large-scale applications, fluid layers may be applied with large-scale coating machinery, including roll coaters, curtain coaters, gravure and reverse gravure devices, and any of the coating devices known in the art. Sprayers may be used at any scale, especially for lower-viscosity primers or polymerizable monomer layers.

Application techniques and devices may be combined, as in applying fluid from a syringe, and then rubbing it into the surface with a finger tip. Such operations may be repeated, as in applying drops of priming initiator; rubbing these into the surface with a brush; repeating  
5 this operation; adding monomer solution; rubbing it in; and finally applying additional layers of monomer before or during the application of curing means, such as light, heat, or slow release of peroxide radicals.

An additional application means which is required in many coating techniques described herein, and in particular in the preferred coating  
10 method which uses photoinitiation to cure the monomer, is a light source. For large-scale application, flood lamps and similar devices are useful. In small, localized applications, such as tissue sealing and coating, it may be preferable to use a localized source such as a fiber optic or light guide, which can project radiation of the appropriate wavelength onto the site to  
15 be treated to cause polymerization of the monomer. Also, a light emitter could be carried on a device, as a miniature bulb. A focused beam from a remote source could be suitable if, for example, the surface was exposed. In exposed surfaces, it is possible that ambient light could be sufficient to polymerize the coating, especially at high initiator levels.

20 Each of the applications means can be separate, so that a kit of application means could contain, for example, one or more containers or reservoirs, one or more pads or brushes, and if required at least one light guide. The application means could also be combined in whole or in part. For example, a dripping device, such as a tube, could be combined with a  
25 spreading device, such as a brush. These could further be combined with a light guide. Such combination devices are especially desirable in treatment of living organisms, and especially humans, to maximize the simplicity of a procedure and the probability of correctly conducting it.

#### COMPLIANCE PROPERTIES

30 The compliance properties of the material herein described are those of the material after it has polymerized to form a polymerized material. As used herein, "polymerized material" includes material which

forms by the ionic or covalent reaction of monomer precursor molecules. Preferably, the polymerized material is formed by covalent reactions of the monomers. It can be very difficult to measure the elastic properties of the material when adhered to tissue. The mechanical properties are therefore  
5 when appropriate measured on samples made *in vitro*, either in a mold, or, as in the lap-shear test, in contact with standardized tissue. Such measurements must be corrected to conditions applicable to tissue treatment, including the diluting effects of polymerization reagents, or of fluids on the tissue. Thus, a sealing solution may be applied to tissue at a  
10 concentration of 30%, but in the coating process it may be diluted to 15% effective concentration by dilution with blood or plasma. Similarly, especially in the case of fibrin sealant, the polymer concentration may be reduced by mixing with polymerizing reagents, either in bulk or by spraying. Where appropriate, such corrections have been taken into  
15 account in the descriptions herein. Materials may be equilibrated with water before testing either by absorption or syneresis.

In light of these observations, an effective material for forming a compliant coating or sealant preferably has a strain or elongation before fracture substantially similar to or at least as great as the expected strain  
20 during normal use of the tissue to which it is applied, and the elongation of the polymerized material is preferably reversible. This is to avoid either detachment from the tissue or fracture, or limitation of the tissue's natural expansion. Preferably, the effective compliant material will have a reversible elongation at least about 150% as great, more preferably at least  
25 about 200% as great, and still more preferably at least about 300% as great as the expected strain of the tissue.

The polymerized material thus may be designed and selected for application to different tissue, to have an elongation at rupture which is similar to or greater than the elongation of the tissue *in vivo* during its  
30 function. The elongation at rupture of the polymerized material can be, for example, greater than 100% or 200%, or optionally greater than 300% or 400%. In some embodiments, the elongation at rupture of the

polymerized material may be between for example 100% and 700%, depending on the tissue properties. In some applications, an elongation at rupture greater than 700% is useful.

In addition, the compliant material, for example in sealant applications, preferably should have a normalized compliance that is comparable in magnitude to the normalized compliance of the tissue to which it is applied. The material will be operative even when the material's normalized compliance is much greater than the normalized compliance of the tissue.

In cases where minimal modification of the natural expansion and contraction of a tissue is desired, the preferred range of the normalized compliance ratio extends from about 0.05 to about 3, preferably from about 0.1 to about 2.0, and more preferably from about 0.1 to about 1.0. In some cases, for example when the tissue is lung tissue, a value of the elastic modulus of less than about 150 kPa, preferably less than 100 kPa, more preferably less than about 50 kPa, and most preferably less than about 30 kPa is preferred.

To obtain the desired ratio of the normalized compliance of the polymerized material to the normalized compliance of tissue, the overall force required to stretch the sealant layer should be adjusted, since that of the tissue is fixed. The adjustment can be accomplished by any of several known methods, including the alteration of the thickness of the layer of the polymerized material, or the variation of the polymer concentration, or of the polymer crosslink density, or of other properties of the material. The properties of the precursor materials and the reaction conditions may be adjusted to produce desired other properties of the polymerized material, such as sealant or adhesive properties, or controlled degradation and drug release properties.

Where prevention of tissue deformation is desired, for example during a healing period, the parameters of the tissue coating can be adjusted so that the normalized compliance ratio is significantly in excess of 1.

The adherence of the polymerized material to the tissue is important in order to obtain the benefits of proper compliance properties. An adherence of at least about 20 gm/cm<sup>2</sup> in a single or double lap shear test is preferable for many applications. Use of priming technology,  
5 described elsewhere in this application, is an effective method for obtaining such values. In some applications, such as the use of the polymerized material as a tissue sealant, adherence values of about 30 gm/cm<sup>2</sup> are preferred, and values at or above 40 gm/cm<sup>2</sup> are more preferred.

10 In many applications, such as tissue sealing, the viscosity of the precursor materials can be tailored to obtain optimal coatings. Higher viscosities can favor retention of the uncured or unpolymerized sealant at the site of application, and minimize displacement of the sealant by the presence of bodily fluids at the surface. However, higher viscosities make  
15 the material more difficult to apply. A suitable range of viscosity, for example, for the sealant portion of a sealing system is in the range of about 200 cP (centipoise) to about 40,000, preferably about 500 to about 5000 cP, and more preferably about 700 to about 1200 cP. For lung, a suitable range of viscosity is about 900 to 1000 cP. The optimal viscosity  
20 will depend on the site of application and the nature of the condition which is to be alleviated by the application of the material.

The present invention will be more fully understood by reference to the following non-limiting examples.

**Example 1: General Synthesis of Macromers: Melt Method.**

25 Methods analogous to those described in U.S. Patent No. 4,526,938 to Churchill et al. were used to form derivatized PEG by the melt method. Polyethylene glycol (PEG) was obtained commercially. The molecular weight listed on the label was assumed to be the molecular weight of the material. The PEG was optionally dissolved in methanol and purified by  
30 passage over an ion exchange resin, and dried.

Purified or as-supplied PEG was charged to a reactor, optionally with a small amount of xylene, and heated for five to six hours at about

110°C (note: all temperatures herein are in degrees Celsius) under vacuum to complete removal of water. After cooling under vacuum, the flask was placed in a glove bag, the materials for forming the biodegradable linkages (including T (trimethylene carbonate) and L (lactide)) were added to the  
5 PEG, and the temperature was raised to about 160-165°C under an argon blanket.

After dissolution of the reactants in the melted PEG, a catalyst, typically stannous octoate, was added, the temperature was raised to 185°C, and ring-opening addition was allowed to proceed for about 3  
10 hours, with stirring under argon. The PEG-(T,L) intermediate could be further reacted at this stage, but typically was freed of unreacted monomers by precipitation in hexane, recovery and drying.

The purified intermediate, for example, PEG-(T<sub>n</sub>L<sub>m</sub>), where "n" is the number of T groups and "m" is the number of L groups, or the  
15 original reaction mixture without purification, was taken up in toluene, and an agent capable of adding unsaturated linkages, such as acryloyl chloride, was added, typically in excess, under mild heating (e.g., about 50°C) and in the presence of an acid-neutralizing agent such as triethylamine. Suitable reactant ratios were found to be 1 ml acryloyl chloride and 1.8  
20 ml triethylamine per 30 grams of PEG. The endcapped macromer, PEG-(T,L)-A<sub>2</sub>, was purified by precipitation in hexane, recovered and dried. Stabilizer was optionally added at this stage. The extent of incorporation of monomers was determined by NMR.

A similar procedure was used to prepare other macromers.  
25 PEG-(T<sub>n</sub>)-A<sub>2</sub>, PEG-(D<sub>n</sub>, G<sub>m</sub>)-A<sub>2</sub>, where D is dioxanone and G is glycolide, and like materials were formed by similar procedures. Synthesis of macromers based on other starting hydrophilic blocks follows similar procedures, with adjustment in precipitation conditions as required. In a synthesis with multi-hydroxy compounds, such as polyvinyl alcohol, the  
30 water would be removed azeotropically under mild reflux in, e.g., toluene; and the degradable linkages are preferably synthesized by polymerization onto the hydroxy compound as described above, although such blocks

could be added as preformed activated acrylated blocks, for example, using a carbodiimide derivative of the acylated poly(degradable linkage), if greater control were required.

**Example 2: Synthesis of PEG-TMC and PEG-TMC-Lactide Macromers.**

5

35K(T8)A2 ("35KT" in the examples below) was made from purified PEG of nominal molecular weight 35,000 Daltons by the melt procedure as described above. T was charged into the reactor at a nominal molar ratio of 13:1 to the PEG to obtain this result. The final actual acrylate incorporation averaged 1.6 per PEG molecule, or about 2 acrylates per macromer.

10

35K(T7L2)A2 ("35KTL") contained about 7 T units (6.88 measured) and 2 lactate units (1.86 measured) as synthesized. (Note that there are 2 lactate units per lactide molecule.) T and L were charged at nominal molar ratios of 10:1 and 3:1 relative to PEG.

15

20K(T30L15)A2 contained about 30 T units and 15 lactide units per 20,000 Daltons PEG molecule. The actual acrylate to PEG ratio was 1.42.

20

**Example 3: Seal pressure test on latex to measure strength and elasticity**

25

Poly(ethylene glycol)-lactide-trimethylene carbonate terpolymers endcapped with acrylate esters were evaluated using a seal pressure test apparatus to determine the failure pressure for coatings prepared using the macromers.

30

One of the materials tested had a poly(ethylene glycol) molecular weight of 20,000 Daltons ("20 kiloDaltons"), a lactate incorporation of 13.8 and a trimethylene carbonate incorporation of 16.0, with nominal acrylation of 2 per macromer ("20KTL"). Also tested were 35 kiloDalton PEG esterified with about 8 TMC linkages and then endcapped with acrylates ("35KT"), and 35 kiloDalton PEG esterified with about 8 TMC and about 8 lactate groups ("35 KTL"), both also acrylated. The reagents applied were "primer" and "sealant". The complete system contained both

a photoinitiation system (Eosin Y/triethanolamine) and a redox initiation system (ferrous gluconate/fructose, plus t-butylhydroperoxide after mixing) which did not cause significant polymerization of the macromer until both mixed (primer and sealant) and activated by light.

5           Primer solution contained Eosin Y (2000 ppm, w/w), 5000 ppm ferrous gluconate, 10,000 ppm (1%) fructose, 30,000 ppm NaCl, and 30% w/w of 3.5KL5 macromer (made according to US 5,410,016). Primer was applied to a 2 cm x 2 cm piece of latex film (from a latex examination glove; about 1 mm thick) with a 6 mm diameter hole created in the center.

10          A toroidal Teflon® fluoropolymer template with a 1 cm. diameter central hole was placed on the latex film to control the area of application of the sealant, by limiting its spread.

            Sealant solution contained macromer (in this example, 10% or 20% w/w of one of the macromers described above) dissolved in an aqueous  
15          solution containing isotonic saline, 90 mM triethanolamine as buffer and electron transfer component, Eosin Y (20 ppm) as a photoinitiator, 4000 ppm vinylcaprolactam as comonomer, and 125 ppm t-butylhydroperoxide as part of the light-sensitized redox initiation system. Two drops of  
20          sealant were dispensed inside the template above the hole and then carefully mixed in with the primer, using a brush. Three more drops of sealant were dispensed, and then the area was illuminated with visible light from a xenon arc lamp (450-550 nm) at an intensity of 100 mW/cm<sup>2</sup> for 40 seconds. Samples were placed in phosphate buffered saline (pH 7.4) at 37°C for different times (t=0, 4 hours, 1 days, 3 days, 6 days and 10  
25          days).

            Samples were evaluated at each time point using a seal pressure test apparatus to determine the failure pressure. The test apparatus was a modified membrane holder, in which the latex sample was clamped at the edges between gaskets. Pressure was then applied to the side of the latex  
30          away from the polymer seal, and the pressure required to rupture the seal was measured.

Figure 1 shows the results obtained with five different sealant materials. The seal pressure decreases over the course of time, presumably due to a combination of swelling of the hydrogel due to hydration and programmed degradation of the hydrogel.

5 **Example 4: Bioabsorption in-vivo**

Poly(ethylene glycol)-trimethylene carbonate copolymers, optionally containing lactate, and endcapped with acrylate esters, were evaluated. Two of the materials described in Example 3 were used (20KTL and 35KT). The macromers were polymerized using visible light illumination  
10 from a xenon arc lamp (450-550 nm) at an intensity of 100 mW/cm<sup>2</sup> in a sealant solution containing macromer, eosin, triethanolamine, vinylcaprolactam, t-butylhydroperoxide and saline as in Example 3. Macromer concentration was 10% for 20KTL and 20% for 35KT.

The absorption of the sealant was determined by subcutaneous  
15 implants in rats. Five female Sprague Dawley rats (250-300 g) were used in this study. The animals were anesthetized by intramuscular ("IM") injection of 3.2 ml/kg mixture of Ketamine (52.4 mg/kg), Xylazine (2.8 mg/kg), Acepromazine (0.7 mg/kg). Four 1 cm longitudinal incisions were made through the skin on the back. Two incisions were made on  
20 each side of the spinal column, spaced 1 cm off the midline and 2 cm apart. A 2 X 2 cm pocket was created at each incision site by blunt dissection. Preformed hydrogel disks were prepared using sterile technique. One hundred microliters of sealant solution was placed in the bottom of one well of a standard 24-well tissue culture plate, and was  
25 illuminated for 40 sec at 100 mW/cm<sup>2</sup>, producing a thin disc about 18 mm. in diameter. One disk was placed in each subcutaneous pocket. Incisions were then closed with surgical staples. Animals were euthanized at intervals by CO<sub>2</sub> inhalation. Incisions were opened and gross observations were recorded. Each site was harvested and analyzed by gel  
30 permeation chromatography for mass loss.

Figures 2A and 2B show that the 20KTL based hydrogels were completely absorbed in 20 days *in vivo* (Figure 2A), whereas the 35KT

based hydrogels were partially absorbed (60% weight loss) in 154 days (Figure 2B). This illustrates the significant effect of rapidly-degrading linkages such as lactate groups.

**Example 5: Sealing of Dural Leak in Canine Craniotomy**

5           A poly(ethylene glycol)-trimethylene carbonate-lactate copolymer endcapped with acrylate ester (20KTL, from Example 2) was evaluated for its ability to seal fluid leaks in membranes *in vivo*. The poly(ethylene glycol) molecular weight used was 20,000 Da. The lactate incorporation was 13.8 and the trimethylene carbonate incorporation was 16.0. The  
10          macromer was fully acrylated.

          The performance of the sealant was evaluated in a dural incision injury model in three mongrel canines. The animals were pre-anesthetized, intubated and maintained on isoflurane gas anesthesia. With the head elevated, a bilateral craniotomy was created. Two dural incisions, each 2  
15          cm. long, were made, one on the left side and one on the right side. Incisions were closed using 3 simple interrupted 4-0 to 6-0 silk sutures spaced approximately 5 mm apart. Cerebrospinal fluid (CSF) pressure was raised by inflating the lungs to 20 cm H<sub>2</sub>O, and the leak was assessed. All incisions were found to leak, as expected from the closure.

20          The control side (left) received no additional closure of the incision. For the treatment side (right), the primer (a low-viscosity solution; described in example 4) was applied and mixed with the fluid on the tissue interface. The sealant (10% w/w solution of 20KTL (described above) with other materials as in Example 4) was layered over the primer,  
25          and the primer and sealant were mixed with a brush. Illumination for 40 sec. with a visible xenon arc lamp (450-550 nm) at an intensity of 100 mW/cm<sup>2</sup> was then performed to complete the polymerization.

          The leaks were re-verified by raising the CSF pressure by inflating the lungs to 20 cm H<sub>2</sub>O. Leakage was observed on the control side, but  
30          not on the experimental side. The bone flaps were replaced and the incision was repaired.

All animals were euthanized at 21 days and the craniotomy was re-opened. Adhesions between the dura and the bone flap were recorded, and the dura repair sites were inspected for evidence of CSF fluid leaks. Dural repair sites were dissected free from underlying cortical tissue and the presence of adhesions noted. The tissues were harvested, rinsed in saline, and fixed in 10% neutral buffered formalin. Hematoxylin and eosin stained histological sections were taken.

At the time of explant, the control sites showed a slight fibrosis present between the dura mater and calvarium. No inflammation was detected. The sealant was not apparent in two out of three animals and only small amounts were present in the third animal. The dural edges were approximated. Defects in the bone (resulting from the surgery) were filled with fibro-osseous tissue at 21 days, in both control and treated sites. Normal healing appeared to be taking place, both visually and histologically.

#### **EXAMPLE 6. Solution Synthesis**

Macromers can also be made by synthesis in solution. While requiring additional waste disposal, the solution synthesis is more easily controlled (compared to the melt synthesis of Example 1 or 2), and is preferred for most applications. This example also illustrates the practice of sequential addition of monomers; the method is also useful for simultaneous addition of monomers.

35KTLA was made by dissolving 75 g of 35 kiloDalton (nominal) PEG in toluene to 20% w/w concentration, and was dried by nitrogen purge for 3 hours at 108° C. 3.06 G TMC (14 mole equivalents per PEG) and 0.024 g stannous octoate catalyst were added, and the solution was held at 108° for 4 hours with stirring. Then 0.46 g (1.5 equiv..) lactide was added, and stirring continued for 2 hrs. Then 300 ml toluene was added to give about a 10% wt/vol solution of polymer. After cooling the solution to about 50°, 4.6 g of triethylamine and 2.5 ml of acryloyl chloride were added. The solution was stirred for 20 min. at about 50. Acrylated macromer was recovered by precipitation and

optionally filtration as described in Ex. 1 and 2. The resulting polymer contained 5 TMC residues and 1.2 lactate residues per PEG molecule, and ratios of lactate :acrylate of 0.6.

#### **EXAMPLE 7. In Vitro Degradation**

5           35KTLA2 was synthesized as described in Example 6. The completed macromer had a TMC:PEG molar ratio of 3.57; an acrylate:PEG ratio of 1.52; a lactate: PEG ratio of 1.39; and contained 766 ppm TMC. On gel permeation chromatography, the macromer was 48.1 % "monomer" (one PEG unit per macromer molecule), 46.3 % "dimer" two  
10       PEG units per macromer molecule), 5.4% "trimer" and 0.1 % higher oligomer.

Discs of the macromer were made as described in example 4 and were incubated in phosphate-buffered saline, pH 7.4, at 37° and 57°. At 57°, half of the mass was lost at about 140 hrs, while at 37°, half the mass  
15       was lost at about 42 days. Mass loss was determined by rinsing the specimen, drying to constant weight, and correcting for the amount of buffer and salt present.

#### **EXAMPLE 8. Dioxanone-containing Macromers**

Dioxanone (1,4-dioxan-2-one; p-dioxanone) was synthesized from  
20       DEG (diethylene glycol) essentially according to US 2,807,629, Example 1. Two kilograms of DEG were mixed with 40 g. copper chromite (Aldrich) and heated at about 230° for 4 hours under nitrogen purge, which displaced generated hydrogen. Dioxanone and DEG were distilled from the mixture under vacuum at about 50° pot temperature. DEG was  
25       partially removed by extraction in cold (4°) diethyl ether. The partially purified material was dissolved in chloroform and applied to a silica column equilibrated in chloroform. Dioxanone was recovered in the initial fractions.

Macromer 35KDA was made by drying overnight (vacuum, 110°)  
30       15 g of 35 kiloDalton PEG, 1.7 g dioxanone, and 0.01 g of catalyst (stannous octoate). This is a ratio of 21:1 D:PEG. Samples were also made at other amounts of D (1.0 g, 18:1; 0.84 g, 15:1; 1.34 g, 24:1).

Vials were sealed and heated at 150 for 5 hrs. Samples were dissolved in chloroform; optionally precipitated in ether; and acrylated as described in previous examples. NMR showed final molar ratios in the synthesized polymer of D/PEG, 1.82; Ac/PEG, 1.64.

5           Macromer 35KDLA: To a mixture of 15 g PEG, 0.84 g Dioxanone and 0.01 g catalyst was also added 0.39 g d,l-lactide. The mixture was dried, then incubated at 185 ° overnight; dissolved in chloroform and precipitated in ether, filtered and vacuum-dried; and acrylated with excess acryloyl chloride and triethylamine.

10           In the following Examples 9-10, the following methods and parameters were used. A person of skill in the art can also look to PCT WO 96/29370 for other techniques that may be applicable.

Elongation to fracture and Young's or other elastic modulus.

15           Samples are prepared in a mold to have the required concentration of monomer and other ingredients. The crosslinked or otherwise cured specimens are placed in an appropriate machine, such as an Instron™ tester, and the force required to stretch the sample along a single axis is measured as a function of the distance the sample is stretched (strain). Elongation may be continued until the sample breaks, giving the value for  
20           elongation at break, optionally after cycling at lower elongations to determine the degree of any plastic deformation of the sample. The data (force vs. distance) may be recorded and used to make a plot, as in Figure 3. Because the response of a particular material is not necessarily "ideal", especially at high elongation, a modulus may be calculated from values at  
25           low degrees of elongation where the behavior is closer to linear. Alternatively, the force vs. strain values may be used directly without extrapolation, or without division by sample thickness to give the "normalized compliance" discussed above.

Bulk Compression Modulus.

30           The sample of gel or tissue is placed in a suitable instrument, such as a Perkin-Elmer DMA 7e, and the modulus is measured according to a

standard procedure. A gel sample could also be polymerized directly in the instrument for testing.

#### Adhesive strength.

This was tested by a lap shear test. The test sealant material was used to adhere a 1 cm x 1 cm area of two pieces of test substrate, typically a standardized tissue such as rat peritoneum or pig pericardium. After crosslinking or curing of the test material, the force required to break the adhesive bond was determined using a suitable instrument, such as an Instron™ tester. In one variant of the test, three pieces of substrate were adhered: a center piece, with tab extending in one direction, and a pair of outer pieces with tabs extending in the opposite direction; sealant was used to join all three pieces. Either arrangement also can be used to determine the relative mechanical properties of various samples (i.e., compared to standards) at small displacements, which is useful when only limited sample volume is available.

#### Adherence

Adherence of sealant formulae *in vivo* is determined qualitatively, by the relative resistance of the sealant to displacement from its deposition site by a probe.

#### Viscosity

Viscosity was measured by standard methods, typically in a Brookfield™ viscometer.

#### Seal Pressure Testing

Seal Pressure Testing was performed by punching a 3 mm round hole in a standard tissue, such as pig pericardium, and mounting the tissue as the closure in a test fixture. Sealant was applied to the hole and cured, typically in a spiral pattern, to obtain closure of the hole. Then increasing pressure was applied to the transverse side of the tissue until the plug of sealant was displaced.

#### Sealant Polymerization

In Examples 9-10 below, a preferred formulation of the sealing system was used. When applied to tissue or to a surface to which

adherence was required, the surface was primed with a mixture which contained by weight approximately 65% water, 30.4% of a polymerizable macromer (3.3KL5A2, a 3.5 kD polyethylene glycol backbone carrying an average of 5 lactate groups and end capped with acrylate), 3% NaCl, 1% fructose, 0.5% ferrous gluconate, and 0.2% Eosin Y. The primer was applied to the surface and spread with a brush. Then about 2 volumes of sealant solution was applied and mixed with a brush. The sealant contained about 77% water, 20.5% polymerizable macromer 35KTMC8A2 (35 kD polyethylene glycol carrying an average of 8 trimethylenecarbonate groups and end capped with acrylate), 1.1% triethanolamine, 1% KH<sub>2</sub>PO<sub>4</sub>, 0.4% vinylcaprolactam, 0.013% t-butyl hydroperoxide, and 0.002% Eosin Y. When the sealant solution was tested in isolation, the t-butyl hydroperoxide was omitted. The sealant system was photopolymerized by exposure to blue-green light for about 40 sec.

#### EXAMPLE 9. Elasticity Results.

Using the materials described above, lap shear testing samples were prepared by applying the macromer solution with a cotton swab to a 1 cm X 1 cm area on a 3 cm X 1 cm strip of rat peritoneal tissue, then laying the other strip of the same size on top as to make a sandwich. The sample was then transilluminated from the top and then the bottom for 40 sec each. Lap shear testing was performed using a 12.5 mm gauge length. Tensile testing using a sample size of 45 mm X 10 mm X 5 mm and a 12.5 mm gauge length, was performed. DMA (Perkin Elmer) testing with a sample height of 1.6 mm was performed at 37°C after hydrating for 2 hours in saline at 37°C. A subjective scoring system was used to assess adherence in a goat lung model on a scale from 1-4 (1 = poor adherence & 4 = excellent adherence).

#### In Vitro Testing

This synthetic surgical sealant could be rapidly polymerized with visible light to form a flexible hydrogel. As can be seen from the tensile data in Figure 3, this material showed a completely elastic deformation profile with linear elongation at break in excess of 700%. The

polymerization process of this material and the properties of lung tissue and muscle tissue were studied using the dynamic mechanical tester. It was seen that muscle tissue, as expected, had a higher modulus than spongy parenchymal lung tissue. The sealant material was cured within 40 seconds and reached a final modulus very comparable to that of the lung tissue. This ensures a compliant and persistent adhesive bond. The bond strength was determined using the lap shear test apparatus and the material was seen to form a strong yet flexible bond to tissue. This bond strength is in excess of literature values for fibrin glues in comparable tests.

#### In Vivo Testing

All goats that had undergone the thoracotomy procedure survived the surgery uneventfully. Goats were sacrificed at timepoints of 14 days, 1 month, and 3 months. At all timepoints, the hydrogel was seen to be firm and clear and had an adherence score of 3.0-3.5 out of 4.0. No tissue necrosis was evident. Histological sections of the tissue showed normal healing. The results are shown below in Table 1.

Table 1: In-Vitro Testing Summary

#### **Property; Result**

Compressive modulus at full cure, sealant; 32.4 kPa

Compressive modulus of lung tissue, pig; 27.5  
± 3.4 kPa

Compressive modulus of lung tissue, dog; 28.0  
± 1.9 kPa

Modulus of rat muscle tissue; 73.4 ± 6.8 kPa

Young's modulus at full cure, sealant; 29.4 kPa

Elongation at break, sealant; 788 ± 255.2 %

Sealant lap shear strength; 90.17 ± 18.17 g/cm<sup>2</sup>

**EXAMPLE 10. Comparative Results.**

Tissucol™ sealant is a commercial fibrin sealant used in Europe. It is not at present approved for use in the United States, in part because it is made from human serum and thus may carry infectious agents. Tissucol sealant was used according to its manufacturer's directions. In comparison to the preferred sealant formulation of the previous example, the following results were obtained shown in Table 2:

Table 2: Properties of Sealants

<u>Test:</u>	<u>FocalSeal™</u>	<u>Tissucol™</u>
	<u>Sealant</u>	<u>Sealant</u>
A. Double lap shear	38 ± 6 kPa	10 ± 6 kPa
B. Compression Modulus	32 ± 1 kPa	35 ± 5 kPa
C. Viscosity	≈ 780 cP at 20% conc.	117 cP (fibrinogen)
		1.6 CP (thrombin)
D. Seal Pressure Test	≈ 380 ± 100 mm Hg	≈ 30 ± 20 mm Hg

When applied to a living dog lung, the fibrin sealant had an adhesion score of 1, and leaked on all staple lines at 10-40 mm Hg. It was difficult to apply the fibrin material to a punch-type leak, because air bubbles coming through the leak tended to remove the material before it polymerized. In contrast, sealant adhered to primed tissue with an adhesion of 3.5, and typically withstood 80 mm Hg or more of pressure. Its high viscosity slowed bubble penetration.

The optimal material for lung, as described above, has an elongation at break of over 700%. Other materials were suitable, if less optimal. For non-collapsed lung, a material (20KT8A2) with an elongation at break of 225% was suitable, while a material (8KL5A2) with an elongation at break of 100% (and an elastic modulus of 47 ± 4

kPa) was not effective in lung. The expansion of a dog lung was measured. It was found that the effective area expansion during a normal breathing cycle is about 200%, while the expansion from the atelectatic (collapsed) state to full inflation changed area by about 300%. In the  
5 latter case, an extension (strain) of about 100% was observed along one axis, and about 200% along a perpendicular axis, implying non-uniformity of the tissue structure.

Thus, an important requirement for a sealant system on this tissue appears to be that the normalized compliance of the sealant is greater than  
10 the normalized compliance of the tissue to which it is applied. While the lung is perhaps the most dramatic example of tissue elasticity and area expansion during normal physiological processes, other tissues, such as the bowels, the bladder and large arteries, can change surface area substantially during normal physiological cycles. Other tissues, such as the  
15 beating heart, exhibit significant changes in shape (shear) without necessarily changing local area.

The compliance of the sealant may be selected depending on the tissue to which it is to be applied. A sealant having a high value of normalized compliance, or a low value of the normalized compliance ratio  
20 (tissue /material), may be beneficial for certain applications. For example, the 700% -elongation low-modulus material described above is also suitable for sealing the dura of the brain, or the spinal cord after laminectomy, even though these tissues are relatively non-compliant (i.e., are difficult to stretch). Thus, high normalized compliance sealant appears  
25 to be useful on most tissues, and desirable as a material having a broad range of applications.

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**We claim:**

1. A biodegradable, polymerizable macromer having a solubility of at least one gram/liter in an aqueous solution at a temperature in the range between about 0 and 50°C comprising at least one water-soluble region, at least one biodegradable region, and at least one reactive polymerizable group or region capable of crosslinking with other macromers, wherein the polymerizable regions are separated from each other by at least one biodegradable region, and wherein at least one biodegradable region comprises a carbonate or dioxanone linkage.
2. The macromer of claim 1 wherein the water soluble region is attached to a biodegradable region and at least one polymerizable group or region is attached to the biodegradable region.
3. The macromer of claim 1 wherein the water soluble region forms a central core, at least two biodegradable regions are attached to the core, and at least two polymerizable groups or regions are attached to the biodegradable regions.
4. The macromer of claim 1 wherein the biodegradable region is a central core, and at least one polymerizable group or region is attached to the core so that each polymerizable group or region is separated from each other polymerizable group or region by at least one biodegradable region.
5. The macromer of claim 1 wherein the water soluble region is a macromer backbone, the biodegradable region is a branch or graft attached to the macromer backbone, and at least two polymerizable groups or regions are attached to the biodegradable regions.
6. The macromer of claim 4 having two or more polymerizable groups or regions attached to the core.

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7. The macromer of claim 1 wherein the water soluble region is a star backbone, the biodegradable region is a branch or graft attached to the water soluble star backbone, and at least two polymerizable groups or regions are attached to one or more biodegradable branch or graft, so that each polymerizable group or region is separated from each other polymerizable group or region by at least one biodegradable region.

8. The macromer of claim 1 wherein the biodegradable region is a star backbone, the water soluble region is a branch or graft attached to the biodegradable star backbone, and two or more polymerizable groups are attached to the biodegradable backbone so that each polymerizable group or region is separated from each other polymerizable group or region by at least one biodegradable region.

9. The macromer of claim 1 wherein the water soluble region is also the biodegradable region.

10. The macromer of claim 1 wherein the water soluble region is also the biodegradable region, and one or more additional biodegradable regions are grafts or branches upon the water soluble region.

11. The macromer of claim 1 comprising a water-soluble core, at least two biodegradable extensions on the core, and an end cap on at least two extensions, wherein

the core comprises poly(ethylene glycol);

at least one of the extensions comprises a biodegradable carbonate or dioxanone linkage; and

each end cap comprises a group or region which is polymerizable by a free-radical reaction.

12. The macromer of claim 11 wherein at least one of the extensions comprises a biodegradable poly(hydroxy acid).

13. The macromer of claim 12 wherein the poly(ethylene glycol) has a molecular weight between about 400 and 40,000 Da;

the poly(hydroxy acid) oligomers have a molecular weight between about 200 and 2000 Da; and

the polymerizable group or region has a molecular weight between about 50 and 200 Da.

14. The macromer of claim 13 wherein the poly(ethylene glycol) oligomers have a molecular weight of about 20,000 Da; the poly(hydroxy acid) oligomers have a molecular weight about 1000 Da; and the polymerizable groups have a molecular weight of about 50 Da.

15. The macromer of claim 1 wherein the polymerizable group contains a carbon-carbon double bond capable of cross-linking and polymerizing macromers.

16. The macromer of claim 1 wherein crosslinking and polymerization of the macromer are initiated by a light-sensitive free-radical polymerization initiator with or without a cocatalyst, further comprising a free radical polymerization initiator.

17. The macromer of claim 16 wherein the initiator is selected from the group consisting of xanthine dyes, acridine dyes, thiazine dyes, phenazine dyes, camphorquinone dyes, and acetophenone dyes.

18. The macromer of claim 17 wherein the initiator is selected from the group consisting of eosin, ethyl eosin, 2,2-dimethyl-2-phenyl acetophenone, and 2-methoxy-2-phenyl acetophenone.

19. The macromer of claim 1 wherein crosslinking or polymerizations are initiated *in situ* by light having a wavelength of 320 nm or longer.

20. The macromer of claim 1 wherein at least one biodegradable region is selected from the group consisting of poly(alpha-hydroxy acids), poly(lactones), poly(amino acids), poly(anhydrides), poly(orthoesters), and poly(phosphoesters).

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21. The macromer of claim 20 wherein the poly(alpha-hydroxy acid) is selected from the group consisting of poly(glycolic acid), poly(D,L-lactic acid) and poly(L-lactic acid).

22. The macromer of claim 20 wherein the poly(lactone) is selected from the group consisting of poly(epsilon-caprolactone), poly(delta-valerolactone) and poly(gamma-butyrolactone).

23. The macromer of claim 1 wherein the water soluble region is selected from the group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidone), poly(ethyloxazoline), poly(ethylene oxide)-co-poly(propylene oxide) block copolymers, polysaccharides, carbohydrates, proteins, and combinations thereof.

24. The macromer of claim 1 further comprising a prophylactic, therapeutic or diagnostic agent.

25. A method for forming a polymeric, biocompatible coating on tissue comprising:

a) applying to the tissue surface a polymerization initiator capable of initiating polymerization via free radical or cationic polymerization;

b) applying to the initiator-coated surface a solution of a biodegradable, polymerizable macromer with a solubility of at least one gram/liter in aqueous solutions at a temperature in the range between about 0 and 50°C comprising at least one water soluble region, at least one biodegradable region, and at least one functional group capable of being polymerized via free radical or cationic polymerization, wherein the polymerizable groups or regions are separated from each other by at least one biodegradable region and wherein at least one biodegradable region is a carbonate or dioxanone region; and

c) polymerizing the macromer.

26. The method of claim 25, wherein the macromer solution further comprises a polymerization initiator capable of initiating polymerization via free radical or cationic polymerization.

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27. The method of claim 25, wherein the tissue is coated to prevent leakage of gases or bodily fluids from the tissue.

28. The method of claim 25 wherein the tissue is coated to prevent adhesion of the tissue to other tissue.

29. The method of claim 25 wherein the tissue is coated and adhered to other tissue during polymerization.

30. The method of claim 25 wherein the macromer solution further comprises a prophylactic, therapeutic or diagnostic agent.

31. The method of claim 25 wherein the initiator binds to the tissue, further comprising removing unbound initiator prior to application of the macromer solution.

32. A method for making a device for controlled release of a prophylactic, therapeutic or diagnostic agent comprising:

a) mixing a prophylactic, therapeutic or diagnostic agent with a solution of a biodegradable, polymerizable macromer with a solubility of at least one gram/liter in aqueous solutions at a temperature between about 0 and 50°C comprising at least one water soluble region, at least one biodegradable region, and at least one functional group capable of being polymerized via free radical or cationic polymerization, wherein the polymerizable groups or regions are separated from each other by at least one biodegradable region and wherein at least one biodegradable region is a carbonate or dioxanone region; and

b) polymerizing the macromer to incorporate the agent within the resulting polymer.

33. The method of claim 32 wherein the polymer is formed into a shape selected from the group consisting of particles, sheets, rods, and nano or microcapsules.

34. The method of claim 32 wherein the macromer is polymerized *in situ* in or on a living tissue.

35. The method of claim 32 wherein the controlled release device is formed on the surface of a medical device.

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36. The method of claim 35 wherein the device is coated after implantation.

37. The method of claim 35 wherein the device is coated prior to implantation.

38. A method for increasing the elasticity of a hydrophilic polymer gel comprising incorporating one or more carbonate linkages into a biodegradable region of a reactive polymer before gelation by reaction of the reactive groups, wherein the resulting polymer has a solubility in water of at least one gram/liter of an aqueous solution at a temperature in the range between about 0 and 50°C, is biodegradable, and wherein each reactive group is separated from each other reactive group by at least one biodegradable linkage.

39. The method of claim 38 wherein the carbonate linkage is prepared from trimethylene carbonate.

40. The method of claim 38, wherein the polymer includes two or more polymer blocks which are linked by linkages comprising carbonate groups to obtain a higher molecular weight of reactive macromer without compromise of biodegradability.

41. A method for improving the biodegradability of a carbonate-comprising chemically-reactive macromer, the method comprising:

- a) reacting a carbonate with a biocompatible compound comprising at least two hydroxyl groups to form a carbonate-comprising precursor for a sufficient time to ensure completion of the reaction and attainment of equilibrium among reacting species;
- b) adding an excess of a reagent forming a biodegradable linkage, wherein the reagent comprises a biodegradable moiety other than a carbonate; and then
- c) adding an additional reagent which forms a chemically-reactive group on the macromer

so that a macromer is formed comprising at least one water-soluble region, at least one biodegradable region, and at least one reactive polymerizable group or region capable of crosslinking with other macromers, wherein the polymerizable regions are separated from each other by at least one biodegradable region, wherein at least one biodegradable region comprises a carbonate or dioxanone linkage, and wherein the macromer has a solubility of at least one gram/liter in an aqueous solution at a temperature in the range of about 0°C and 50°C.

42. The method of claim 41, wherein the carbonate is a cyclic aliphatic carbonate.

43. The method of claim 41 wherein the hydroxyl groups are carried on a biocompatible polymer.

44. The method of claim 43 in which the polymer is a polyalkylene glycol.

45. The method of claim 41 in which the reagent of step b) comprises the residue of a hydroxycarboxylic acid.

46. The method of claim 45 in which the hydroxycarboxylic acid residue is an alpha-hydroxy acid.

47. The method of claim 46 in which the acid is selected from lactic acid, lactide, and lactoyl chloride.

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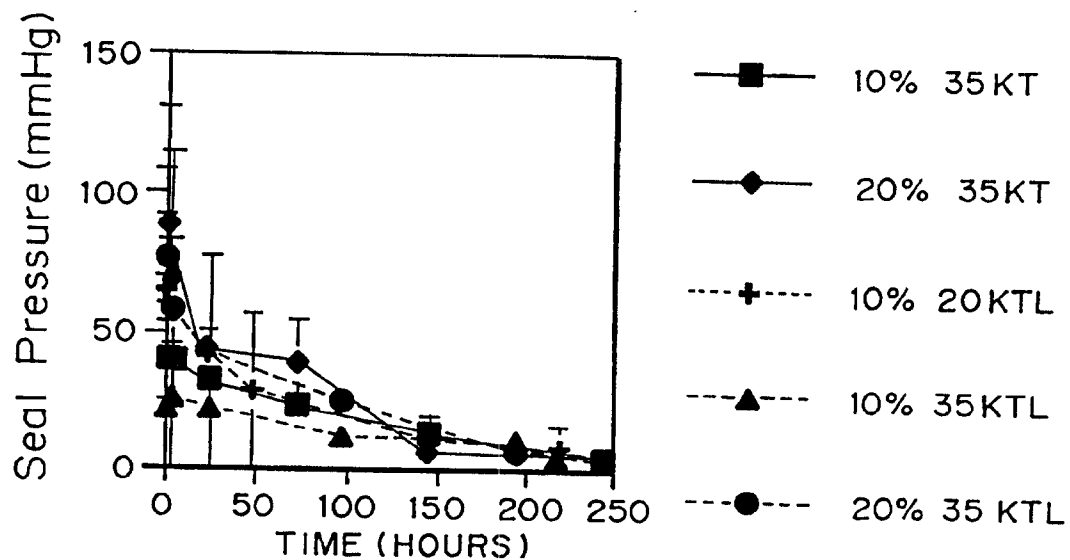


FIG. 1

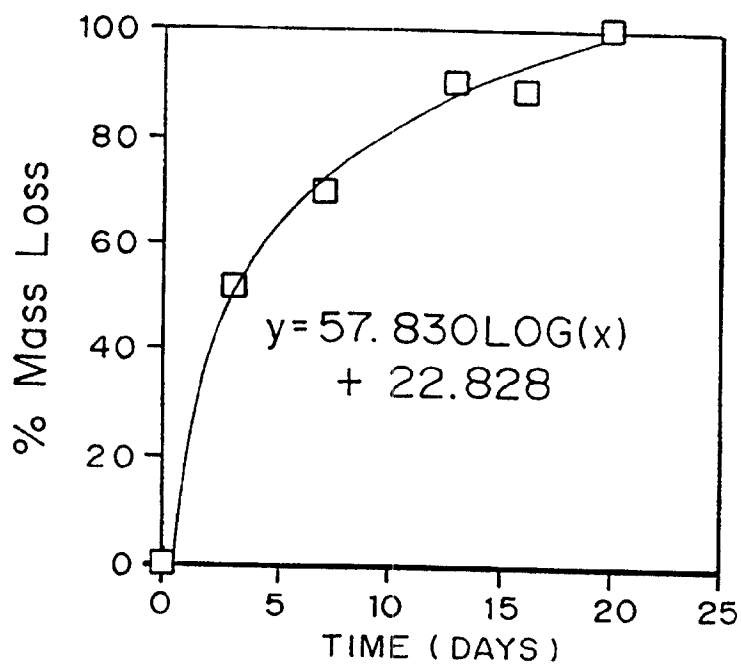


FIG. 2a

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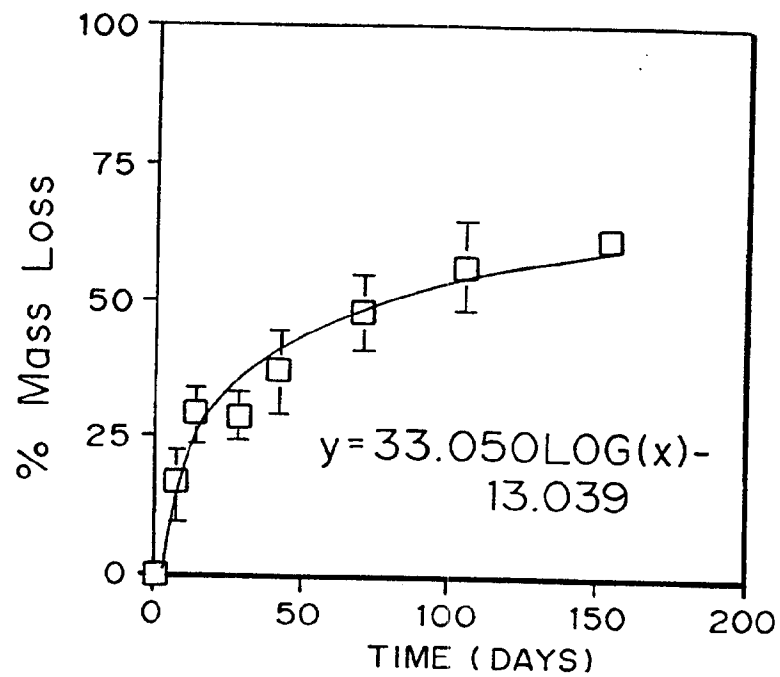


FIG. 2b

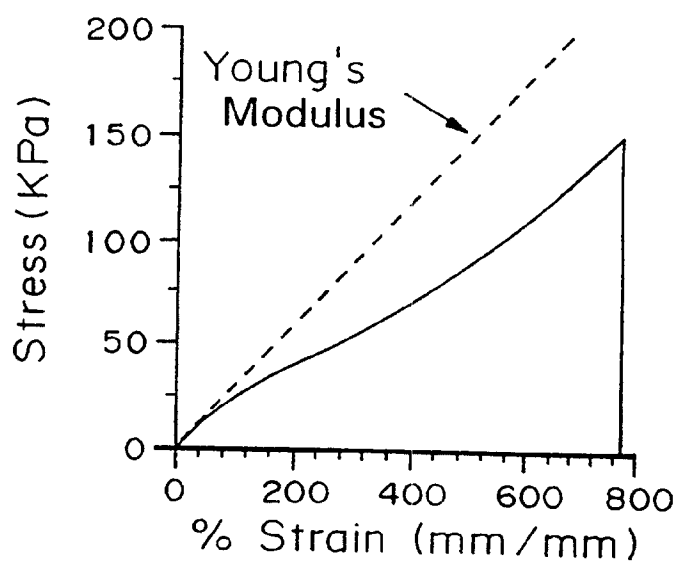


FIG. 3